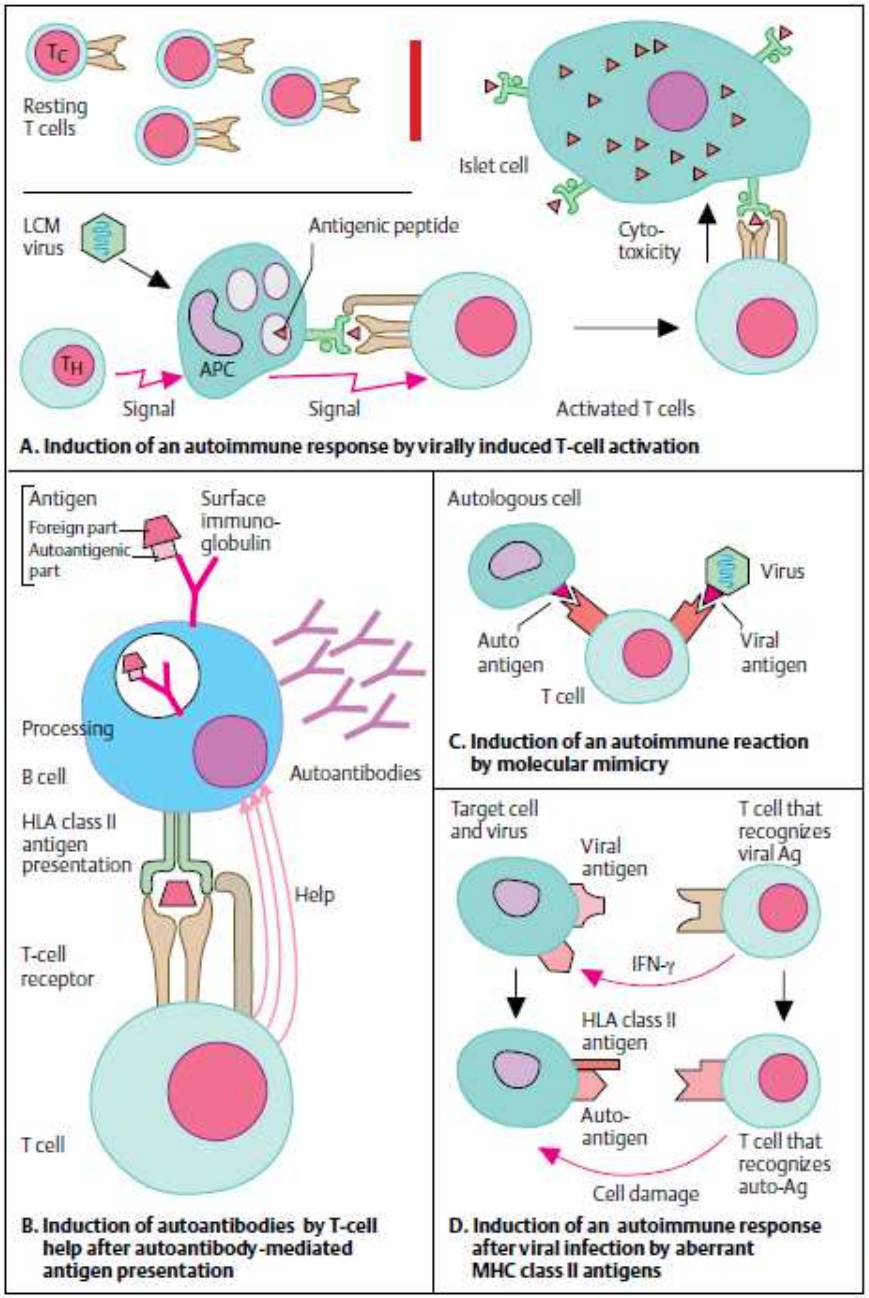
AUTOIMMUNE DISEASES

Kenneth Alonso, MD, FACP

Mechanisms of autoimmunity



Burmester, GR, Pezzutto, A, Color Atlas of Immunology. 2003. Thieme. Stuttgart. p71 Accessed 12/10/2019

Major histocompatibility complex

- Human leukocyte antigen (HLA) genes on short arm (p) of chromosome 6
- Gene products are membrane associated glycoproteins
- HLA related disease does not appear to follow simple Mendelian genetics.

Major histocompatibility complex

- MHC I
- Located on all nucleated cells
- Mature red cells lack a nucleus
- Coded by three genes: A, B, C
- Heterodimer of polymorphic α-chain linked covalently to β-macroglobulin
- α1 and α2 domains (of three) form outward cleft where peptides derived from proteins produced and located in cytoplasm bond
- Viral peptides and tumor antigens
- Peptides recognized by CD8+ cells

Major histocompatibility complex

- MHC II
- Coded by three genes: DP, DQ, DR
- Heterodimer of polymorphic α-chain and polymorphic β-chain
- α_1 and β_1 domains form outward cleft where molecules internalized into vesicles bond
- Extracellular microbes and soluble proteins
- β_2 binding site recognized by CD4+ cells
- APC, Macrophages, B cells as well
- MHC II restricted as co-stimulation required

Table 6-7 Association of HLA Alleles and Inflammatory Diseases

Disease	HLA allele	Odds Ratio†
Rheumatoid arthritis (anti-CCP Ab positive)‡	DRB1, 1 SE allele¶	4
	DRB1, 2 SE alleles	12
Type 1 diabetes	DRB1*0301-DQA1*0501-DQB1*0201 haplotype	4
	DRB1*0401-DQA1*0301-DQB1*0302 haplotype	8
	DRB1*0301/0401 haplotype heterozygotes	35
Multiple sclerosis	DRB1*1501	3
Systemic lupus erythematosus	DRB1*0301	2
	DRB1*1501	1.3
Ankylosing spondylitis	B*27 (mainly B*2705 and B*2702)	100-200
Celiac disease	DQA1*0501-DQB1*0201 haplotype	7

†The odds ratio reflects approximate values of increased risk of the disease associated with the inheritance of particular HLA alleles. The data are from European-derived populations.
‡Anti-CCP Ab = antibodies directed against cyclic citrullinated peptides. Data are from patients who test positive for these antibodies in the serum.
¶SE refers to shared epitope, so called because the susceptibility alleles map to one region of the DRB1 protein (positions 70-74).
Courtesy Dr. Michelle Fernando, Imperial College London.

Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-7 Accessed 12/10/2019

HLA related disorders

HLA type	Disease association
B8	Grave's disease Celiac sprue
B27	Ankylosing spondylitis Psoriasis Reiter's syndrome Inflammatory bowel disease
DR2	Goodpasture's syndrome Multiple sclerosis SLE Narcolepsy
DR3	Celiac disease Myasthenia gravis SLE Grave's disease Addison's disease Type I diabetes mellitus
DR4	Rheumatoid arthritis Pemphigus vulgaris Type I diabetes mellitus
DR5	Hashimoto's thyroiditis Pernicious anemia
DR 7 DR 11 Dw3 Dw4 DQ2	Steroid responsive nephrotic syndrome Hashimoto's disease Celiac disease Sjögren's syndrome Rheumatoid arthritis Type I diabetes mellitus

Table 6-8 Selected Non–HLA Genes Associated with Autoimmune Diseases

Putative Gene Involved	Diseases	Postulated Function of Encoded Protein and Role of Mutation/Polymorphism in Disease
Genes involved in immune regulation:		
PTPN22	RA, T1D, IBD	Protein tyrosine phosphatase, may affect signaling in lymphocytes and may alter negative selection or activation of self-reactive T cells
IL23R	IBD, PS, AS	Receptor for the T_H17-inducing cytokine IL-23; may alter differentiation of CD4+ T cells into pathogenic $T_H17$effector cells
CTLA4	T1D, RA	Inhibits T cell responses by terminating activation and promoting activity of regulatory T cells; may interfere with self-tolerance
IL2RA	MS, T1D	α chain of the receptor for IL-2, which is a growth and survival factor for activated and regulatory T cells; may affect development of effector cells and/or regulation of immune responses
Genes involved in immune responses to microbes:		
NOD2	IBD	Cytoplasmic sensor of bacteria expressed in Paneth and other intestinal epithelial cells; may control resistance to gut commensal bacteria
ATG16	IBD	Involved in autophagy; possible role in defense against microbes and maintenance of epithelial barrier function
IRF5, IFIH1	SLE	Role in type I interferon production; type I IFN is involved in the pathogenesis of SLE (see text)

AS, Ankylosing spondylitis; IBD, inflammatory bowel disease; MS, multiple sclerosis; PS, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
The probable linkage of these genes with various autoimmune diseases has been defined by genome-wide association studies (GWAS) and other methods for studying disease-associated polymorphisms.
Adapted from Zenewicz LA, Abraham C, Flavell RA, Cho JH: Unraveling the genetics of autoimmunity. Cell 2010;140:791.

Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-8 Accessed 12/10/2019

Table 6-1 Mechanisms of Hypersensitivity Reactions

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Immediate (type I) hypersensitivity	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation	Anaphylaxis; allergies; bronchial asthma (atopic forms)
Antibody-mediated (type II) hypersensitivity	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury	Autoimmune hemolytic anemia; Goodpasture syndrome
Immune complex–mediated (type III) hypersensitivity	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Inflammation, necrotizing vasculitis (fibrinoid necrosis)	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction
Cell-mediated (type IV) hypersensitivity	Activated T lymphocytes → (1) release of cytokines, inflammation and macrophage activation; (2) T cell–mediated cytotoxicity	Perivascular cellular infiltrates; edema; granuloma formation; cell destruction	Contact dermatitis; multiple sclerosis; type 1 diabetes; tuberculosis

Ig, Immunoglobulin.

Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-1 Accessed 12/10/2019

Type I reaction Mechanisms

- Immediate exposure to an antigen
- Leads to sensitization of a CD4 cell
- Differentiates into a T_{H2} cell that activate B cells
- IL 4 causes switch from IgM to IgE synthesis
- IL 5 stimulates eosinophil production and activation
- IL13 enhances IgE production and stimulates mucus secretion from epithelial cells

Type I reaction
Mechanisms

- Subsequent exposure to that antigen leads to binding of IgE by high affinity IgE Fc receptors with degranulation of mast cells (or basophils)
- Mast cells may also be degranulated by C5a and C3a (anaphylatoxins)
- Release of histamine and other vasoactive amines
- Edema and bronchoconstriction result.
- Release of leukotriene 4 prolongs inflammatory response (late phase)

Type I reaction

- 50% of patients have a family history of atopy
- 20-30% non-allergic causes
- Urticaria is the localized clinical presentation in the skin.
- Angioedema (facial and laryngeal edema) is life threatening
- Systemic anaphylaxis is also life threatening
- Peanuts
- Shellfish
- Bee venom
- Penicillin
- Antisera
- Desensitization to antigen as a treatment

Table 6-2 Examples of Disorders Caused by Immediate Hypersensitivity

Clinical Syndrome	Clinical and Pathologic Manifestations
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) cause by vascular dilation; airway obstruction due to laryngeal edema
Bronchial asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity; inflammation and tissue injury caused by late-phase reaction
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles

Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-2 Accessed 12/10/2019

Type II reaction Mechanisms

- I. Antibody mediated toxicity to target antigens:
- Complement mediated reactions may promote direct cell lysis
- C3b permits opsonization of the antigen, promoting its phagocytosis.
- Membrane attack complex
- Goodpasture's syndrome (IgG mediated)
- Cold immune hemolytic anemia (IgM mediated)
- Bullous pemphigoid
- Eczematous dermatitis

Type II reaction Mechanisms

- II. Antibody dependent cell-mediated cytotoxicity
- Complement independent
- NK cell destruction of neoplastic and virus infected cells (IgG dependent)
- Eosinophil destruction of helminths (IgE dependent)
- Phagocytosis (IgG dependent)
- Autoimmune hemolytic anemia
- ABO and Rh hemolytic disease of the newborn
- Idiopathic thrombocytopenic purpura

Type II reaction Mechanisms

- III. Antibody mediated cellular dysfunction where the antibody itself affects antibody function.
- Graves' disease (TSH receptor)
- Myasthenia gravis (ACh receptor)

- Inflammation is promoted

Table 6-3 Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Red cell membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of red cells	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (GpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

ANCA, Antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-3 Accessed 12/10/2019

Type III reaction Mechanisms

- Antibody-antigen immune complexes form
- Deposited in tissue.
- Inflammation at site of deposition
- Complement activated
- Serum sickness
- Post-streptococcal glomerulonephritis
- Systemic lupus erythematosus
- The Arthrus reaction is localized vasculitis
- Interstitial lung disease associated with Thermophilic fungi

Table 6-4 Examples of Immune Complex–Mediated Diseases

Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	Nuclear antigens (circulating or "planted" in kidney)	Nephritis, skin lesions, arthritis, others
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Polyarteritis nodosa	Hepatitis B virus antigens in some cases	Systemic vasculitis
Reactive arthritis	Bacterial antigens (e.g., *Yersinia*)	Acute arthritis
Serum sickness	Various proteins, e.g., foreign serum protein (horse antithymocyte globulin)	Arthritis, vasculitis, nephritis
Arthus reaction (experimental)	Various foreign proteins	Cutaneous vasculitis

Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-4 Accessed 12/10/2019

Type IV reaction Mechanisms

- Direct mediation by sensitized T-cells
- I. Previously sensitized T_{H1} cells secrete interferon-γ
- Recruit macrophages.
- Macrophages secrete IL-12
- Promote differentiation of T_{H1} cells.
- Granuloma formation in delayed type hypersensitivity (DTH)
- CD4+, APC MHCII
- PPD
- Multiple sclerosis
- CD8+ MHC I
- Contact dermatitis

Type IV reaction Mechanisms

- II. Previously sensitized CD8 cells kill antigen bearing cells.
- MHC I class molecules required for antigen presentation.
- Perforin-granzyme induced apoptosis or FAS-ligand mediated apoptosis results.
- Polymyositis, dermatomyositis

- Chemical sensitivities may not be immune mediated.

- Transplant rejection may be cell mediated, humoral mediated, or a combination of both.

Table 6-5 T Cell–Mediated Diseases

Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury	Clinicopathologic Manifestations
Rheumatoid arthritis	Collagen? Citrullinated self proteins?	Inflammation mediated by T_H17 (and T_H1?) cytokines; role of antibodies and immune complexes?	Chronic arthritis with inflammation, destruction of articular cartilage
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by T_H1 and T_H17 cytokines, myelin destruction by activated macrophages	Demyelination in CNS with perivascular inflammation; paralysis,
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation, destruction of islet cells by CTLs	Insulitis (chronic inflammation in islets), destruction of β cells; diabetes
Inflammatory bowel disease	Enteric bacteria; self antigens?	Inflammation mediated by T_H1 and T_H17 cytokines	Chronic intestinal inflammation, obstruction
Psoriasis	Unknown	Inflammation mediated mainly by T_H17 cytokines	Destructive plaques in the skin
Contact sensitivity	Various environmental chemicals (e.g., urushiol from poison ivy or poison oak)	Inflammation mediated by T_H1 (and T_H17?) cytokines	Epidermal necrosis, dermal inflammation, causing skin rash and blisters

Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred based on the similarity with experimental animal models of the diseases.

Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-5 Accessed 12/10/2019

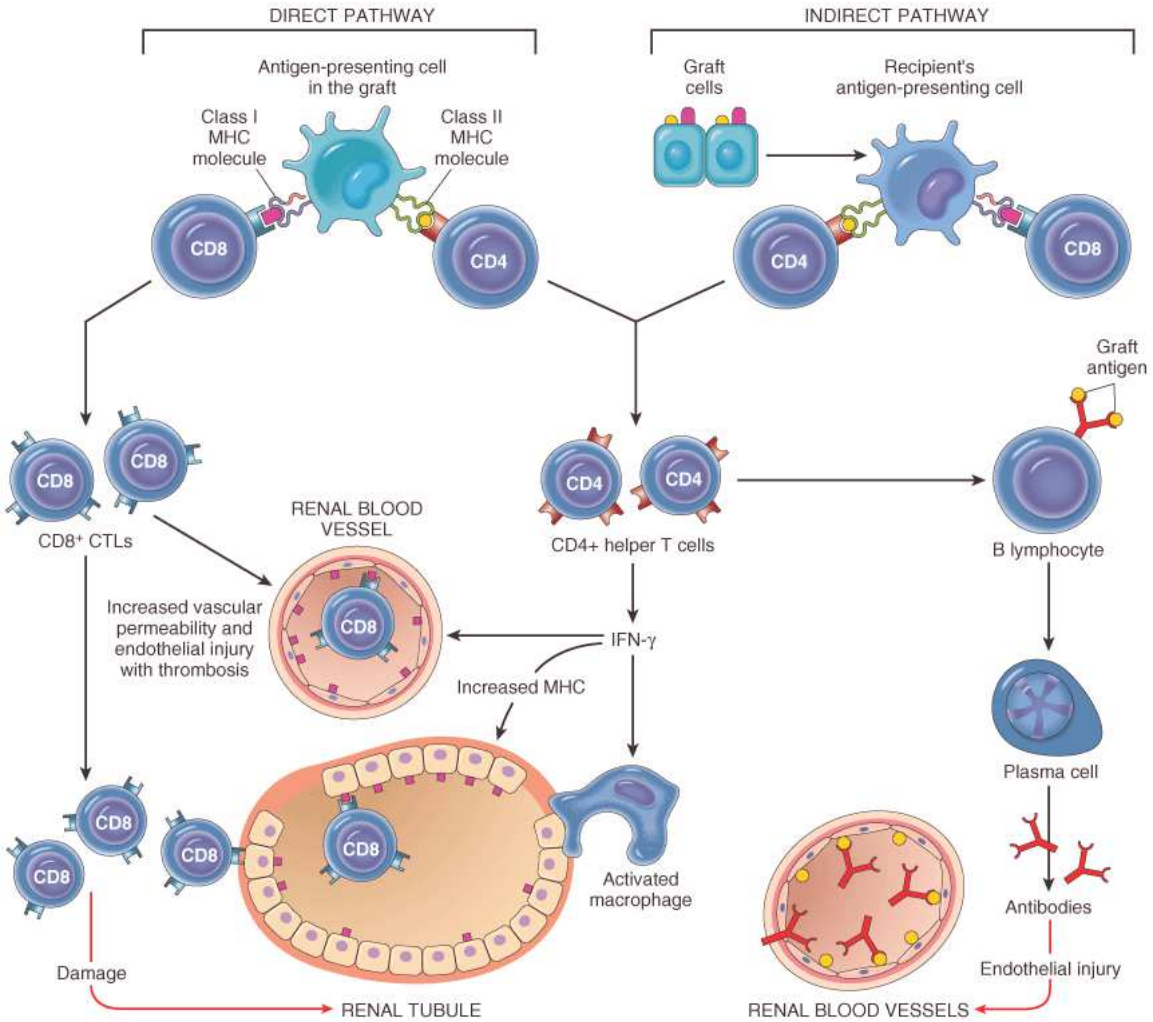
Table 6-6 Autoimmune Diseases

Organ-Specific	Systemic
Diseases Mediated by Antibodies	
Autoimmune hemolytic anemia	Systemic lupus erythematosus
Autoimmune thrombocytopenia	
Autoimmune atrophic gastritis of pernicious anemia	
Myasthenia gravis	
Graves disease	
Goodpasture syndrome	
Diseases Mediated by T Cells*	
Type 1 diabetes mellitus	Rheumatoid arthritis
Multiple sclerosis	Systemic sclerosis (scleroderma)† Sjögren syndrome†
Diseases Postulated to Be Autoimmune	
Inflammatory bowel diseases (Crohn disease, ulcerative colitis)‡	
Primary biliary cirrhosis†	Polyarteritis nodosa†
Autoimmune (chronic active) hepatitis	Inflammatory myopathies†

*A role for T cells has been demonstrated in these disorders, but antibodies may also be involved in tissue injury.
†An autoimmune basis of these disorders is suspected but the supporting evidence is not strong.
‡These disorders may result from excessive immune responses to commensal enteric microbes, autoimmunity, or a combination of the two.

Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-6 Accessed 12/10/2019

Transplant rejection



Fever and organ dysfunction as initial signs

Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig 6-32 Accessed 12/10/2019

Transplant rejection

- Hyperacute
- Preformed circulating antibodies (usually ABO)
- Type II reaction
- Vessel thrombosis threatens graft
- Higher risk in multiparous women
- ABO mismatch transplant donor and recipient
- Acute
- Antibody mediated post-exposure
- Chronic
- Antibody identified in circulation but not in graft
- Vasculitis

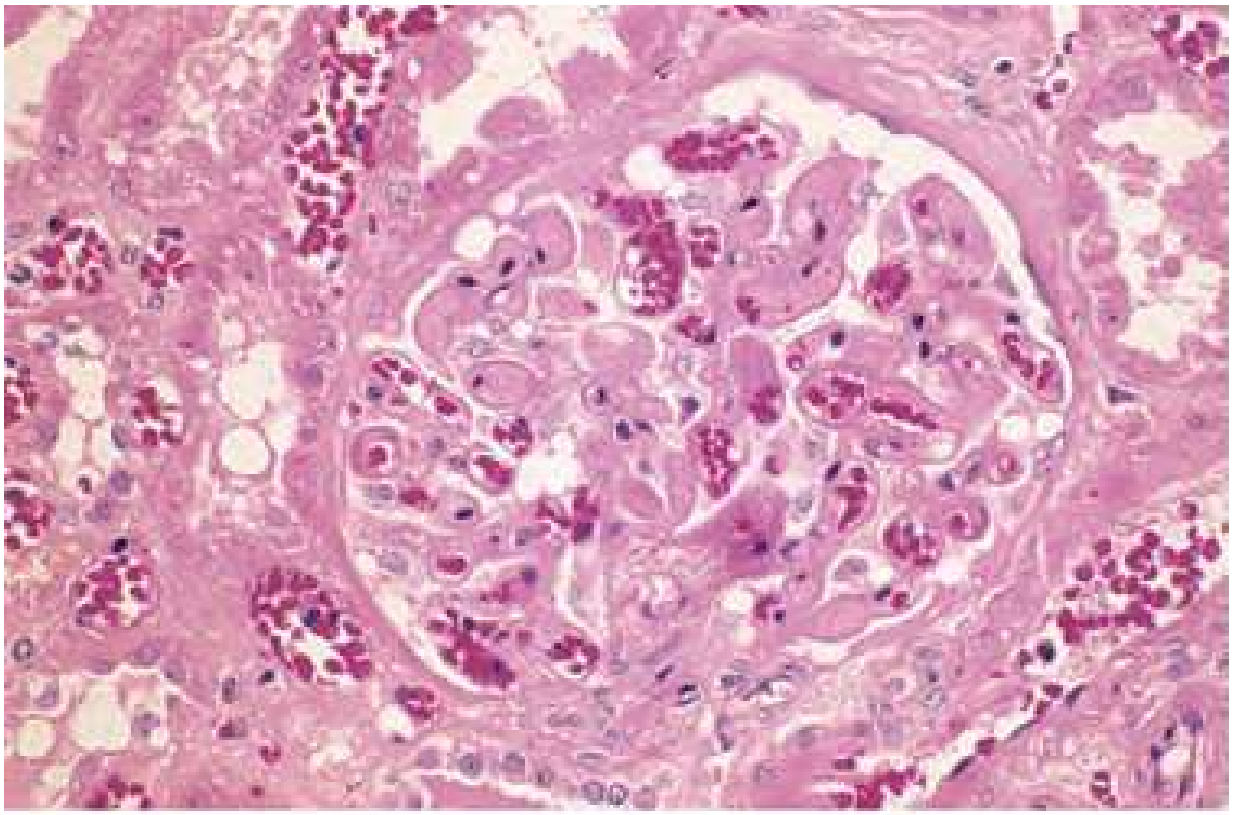
Transplant rejection

- Acute cell-mediated
- Most common
- Type IV reaction
- CD8+, CD4+ cells
- Inflammatory cytokines
- Interstitial and endothelial destruction
- Reversible
- Chronic cell-mediated
- Cytokines that promote fibrosis and endothelial cell proliferation

Hyperacute renal allograft rejection

- Antibody mediated
- Histopathology:
- Intense neutrophil inflammatory infiltrates
- Platelet and fibrin thrombi in glomeruli
- Severe ischemic change
- Immunoglobulin and complement deposited in membranes

Hyperacute rejection



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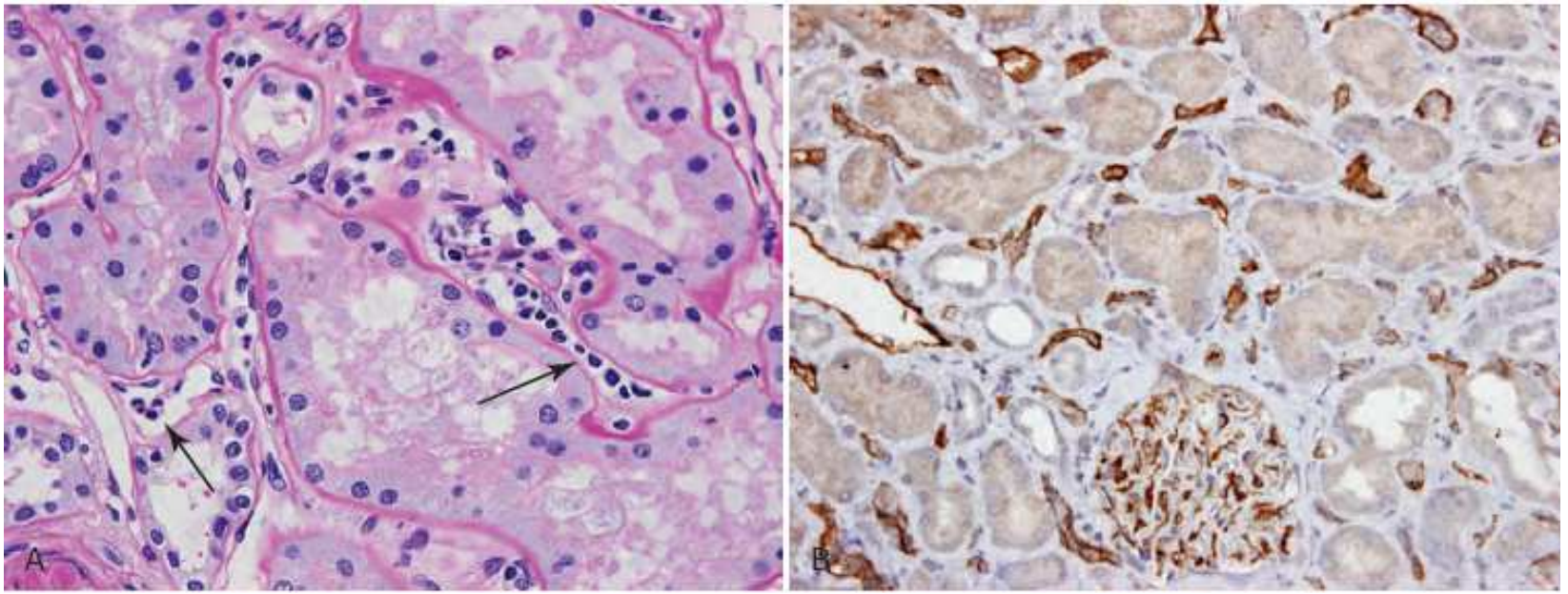
Accessed 12/10/2019

Acute renal allograft rejection

- Antibody mediated
- Histopathology:
- Glomerular and peritubular capillaries pattern
- Inflammation of glomeruli and peritubular capillaries
- C4d deposited

Acute humoral mediated rejection



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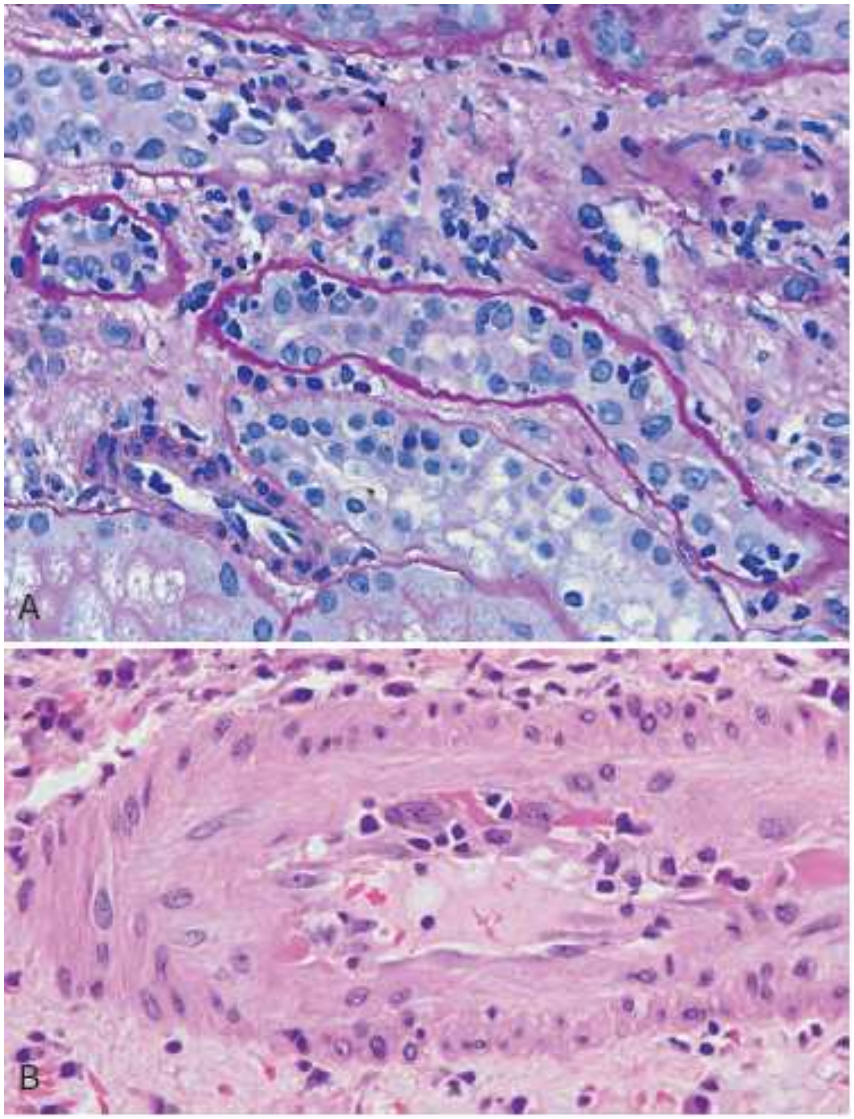
Acute renal allograft rejection

- CD4+, CD8+ mediated
- Histopathology:
- Tubulointerstitial pattern of rejection
- Type I reaction
- Interstitial inflammation with infiltration of tubules
- Type II reaction
- Endothelial inflammation
- Type III reaction
- Necrosis of vessel wall

Acute T-cell mediated rejection

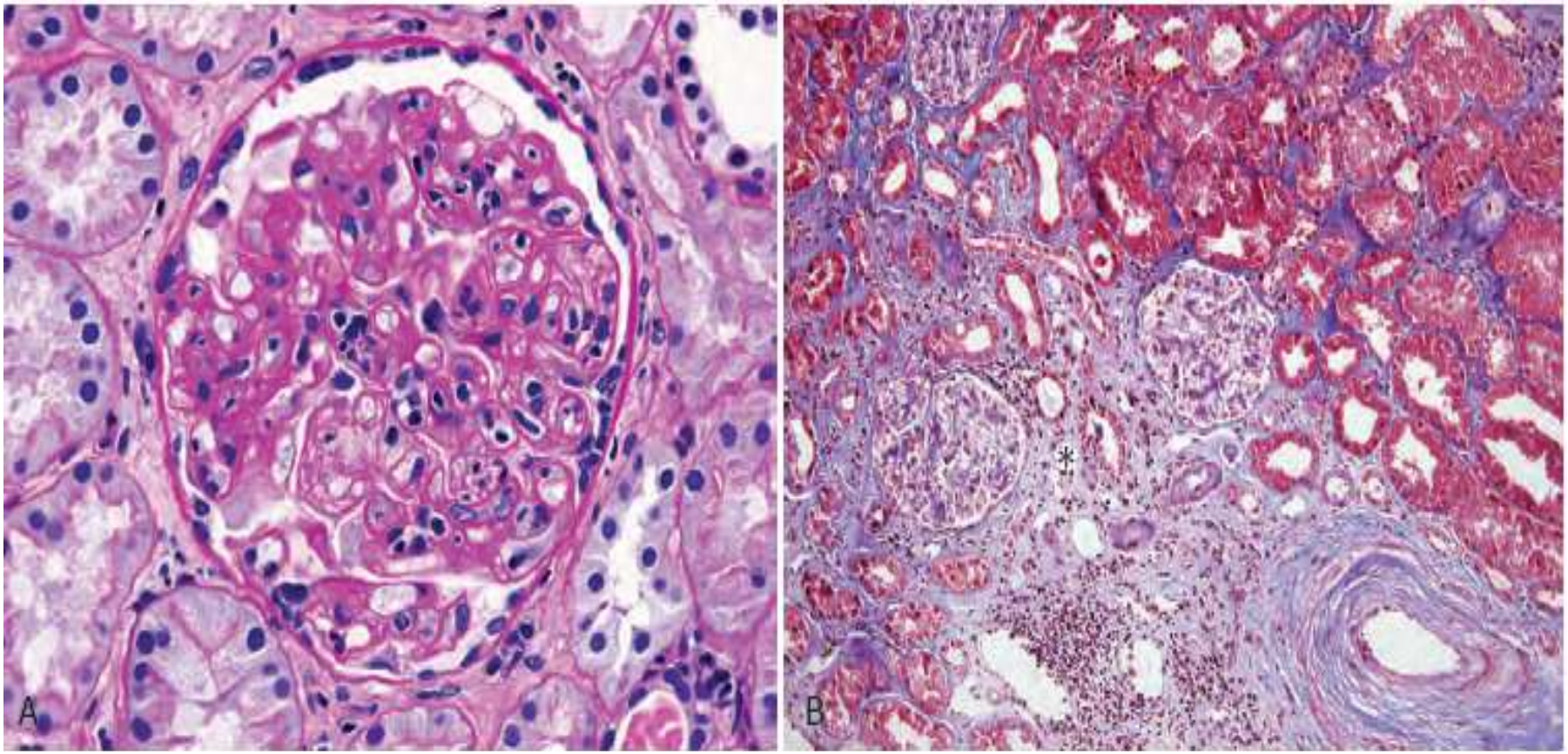


Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig. 6-34
Accessed 12/10/2019

Chronic renal allograft rejection

- Histopathology:
- Intimal thickening of vessels
- Reduplication of glomerular basement membrane
- Multilayering of peritubular capillaries
- Intersititial fibrosis
- Mononuclear cell infiltrates including NK and plasma cells

Chronic rejection



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Accessed 12/10/2019

Match criteria

- ABO match is essential as a mismatch would lead to immediate failure of the transplant.
- For kidney transplants
- HLA match is important.
- In addition to the six antigen crossmatch, HLA-DQ is specifically examined as a mismatch at DQ is associated with poorer graft outcomes.
- 24% of transplanted patients will develop antibodies to donor DQ over a 10 year period.

Match criteria

- 1. When the recipient is placed on the transplant list,
- 2. As well as periodically during the wait for a donor,
- 3. And immediately prior to transplant,
- Tthe recipient is again screened for antibodies to HLA antigens that may attack the transplanted organ.

Is HLA-DQ mismatching associated with graft loss and acute rejection?

CJASN
Clinical Journal of American Society of Nephrology

Cohort

Primary kidney transplants

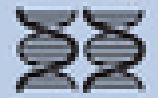
UNOS/OPTN data
2005-2014

N=93,782

4.1 years median follow-up

Predictor

HLA-DQ mismatches



Zero mismatch
N=22,730

1 or 2 mismatch
N=71,052

Adjusted for HLA-ABDR, recipient, donor and transplant factors

Findings

1 or 2 mismatch compared to zero mismatch
aHR and aOR (95% CI)

Death-censored graft loss

Acute rejection at 1 year

Living donor

1.18
(1.07-1.30)

1.14
(1.03-1.27)

Deceased donor

1.05
(0.98-1.12)

1.13
(1.03-1.23)

Cold ischemic time ≤17h

1.12
(1.03-1.21)

Cold ischemic time >17h

0.97
(0.89-1.06)

Conclusions HLA-DQ mismatching is associated with graft loss and acute rejection independent of HLA-ABDR. Cold ischemic time >17 hours appears to obviate the benefit of zero HLA-DQ mismatches.

Napat Leeaphorn, Jeremy Pena, Natanong Thamcharoen, Eliyahu Khankin, Martha Pavlakis, and Francesca Cardarelli. HLA-DQ Mismatching and Kidney Transplant Outcomes. CJASN doi: 10.2215/10660917.

Accessed 12/10/2019

Match criteria

- A living donor kidney may survive 12-20 years
- A deceased donor kidney may survive 8-12 years
- 93% (1 year), 75% (5 year), 48% (10 year) kidney organ survival post transplant
- 96, 85, 64% patient survivals over same time frame
- 99, 92, 79% if live donor used
- Whites and Asians constitute the largest groups of live donors
- Neither age disparity nor the presence of diabetes mellitus in the recipient affects overall graft survival

Match criteria

- Optimal size match between donor and recipient associated with greater graft survival irrespective of HLA status
- <30 kg difference in weight
- <15 cm difference in height
- Race pairing also affects survival
- Antigen subtypes not yet identified
- As there are racial disparities in kidney transplantation in the US for genetic reasons, the US has largely abandoned strict crossmatch criteria in order to increase the number of kidneys available to Blacks.

Match criteria

- For other solid organ transplants
- ABO match and physical size of the recipient are the more important determinants of who receives a transplant.
- The heart, lungs, liver, and pancreas do not survive outside the body for more than 12 hours
- Insufficient time to perform a tissue type on the donor organ prior to transplant (are performed later)
- Matched organs survive longer than do mismatched organs
- For allogenic marrow transplants
- ABO and exact HLA matches are critical

DISEASE EXAMPLES

Angioedema

- Type I response
- 90% present with pruritic, edematous, erythematous plaques and sensation of flushing
- Severe reactions:
- Upper airway obstruction experienced as lump in throat, hoarseness, or stridor
- Lower airway obstruction experienced as tightness in the chest and is manifest as wheezing.
- Associated with increased mortality in asthmatics
- Nausea and vomiting with cramping abdominal pain
- Circulatory collapse as fluid leaves intravascular space
- 10-20% of cases will recur 1+ hours after resolution

Pathophysiology

- Histamine release results in flushing, urticaria, pruritus
- Leukotrienes LTC_4, LTD_4, LTE_4 (all contain cysteine) and prostaglandin D_2 cause bronchoconstriction and increased microvascular permeability.
- Prostaglandin D_2 also causes cutaneous flushing, and attracts eosinophils and basophils to the site of mast cell activation.
- Tryptase can activate complement and coagulation pathways.
- Results in production of the anaphylotoxins, C3a and C5a
- Activation of the kallikrein-kinin system

Angioedema

- Perivascular edema, hyperinflated lungs, eosinophil infiltrates are characteristic findings (at autopsy).
- Scratch test or radioassay against antigens as screen
- Serum tryptase elevated up to 5 hours post episode
- Clue to mastocytosis
- Platelet activating factor correlates with severity

Urticaria

- Pruritic, edematous, erythematous plaques.
- IgE mediated in majority of cases
- Complement mediated
- Serum sickness (anaphylatoxin release)
- Circulating immune complexes (penicillin)
- Physical onset
- 4% dermatographism
- Cold urticaria
- Usually in children
- Solar urticaria
- Histamine mediation

Urticaria

- Cholinergic urticaria
- Exercise to point of sweating
- Flushing, burning, wheezing
- Vibratory urticaria
- Pressure induced direct degranulation of mast cells
- Intense deep dermal inflammatory infiltrate
- Drug induced (non allergic)
- Opiates
- Radiocontrast material
- Antibiotics
- ACE inhibitors
- NSAIDs

Urticaria

- Hereditary Angioedema
- Facial swelling
- Laryngeal edema
- Stridor
- Abdominal pain
- Autosomal dominant
- C1 esterase low
- Angioedema-uriticaria-eosinophilia syndrome

Fever, water retention

Cyclic presentation

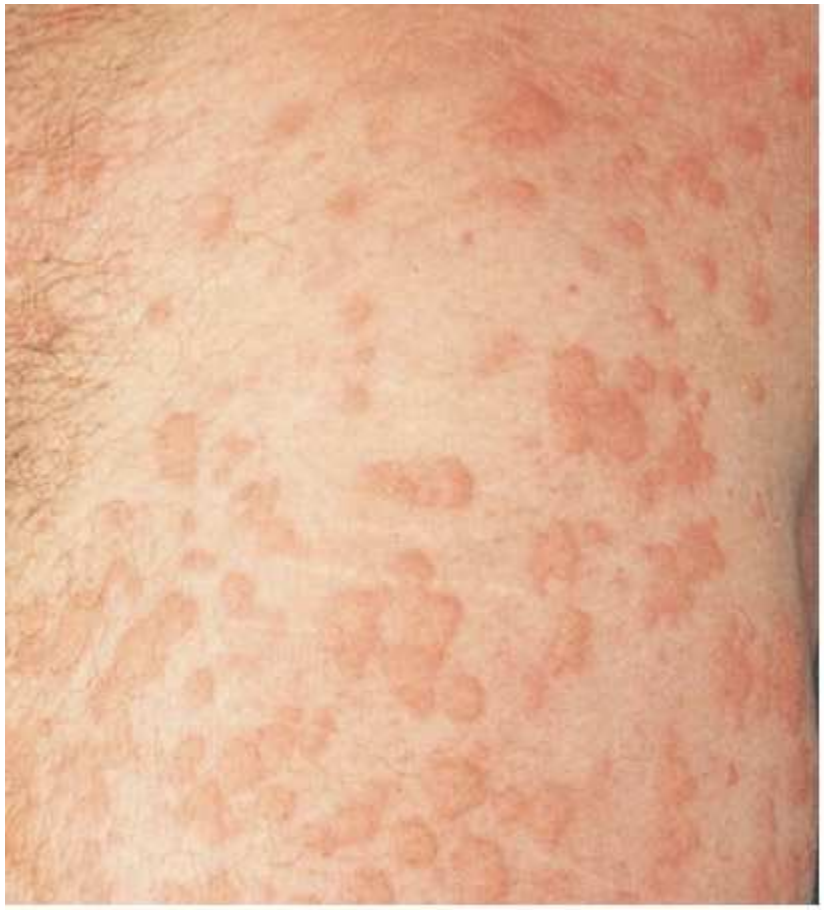
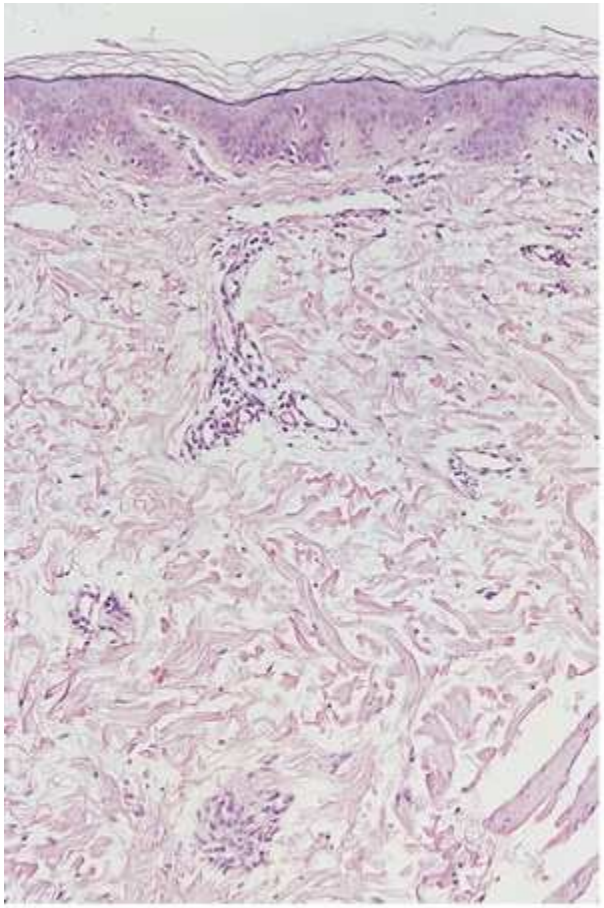


Fig. e-14 Accessed 07/16/2010

Urticaria



A

Characteristic of the reaction is a sparse, perivascular lymphocytic infiltrate with few eosinophils. Note the slight edema in the dermis and around the post capillary venules.

Fig. 6-15A
Accessed 07/16/2010

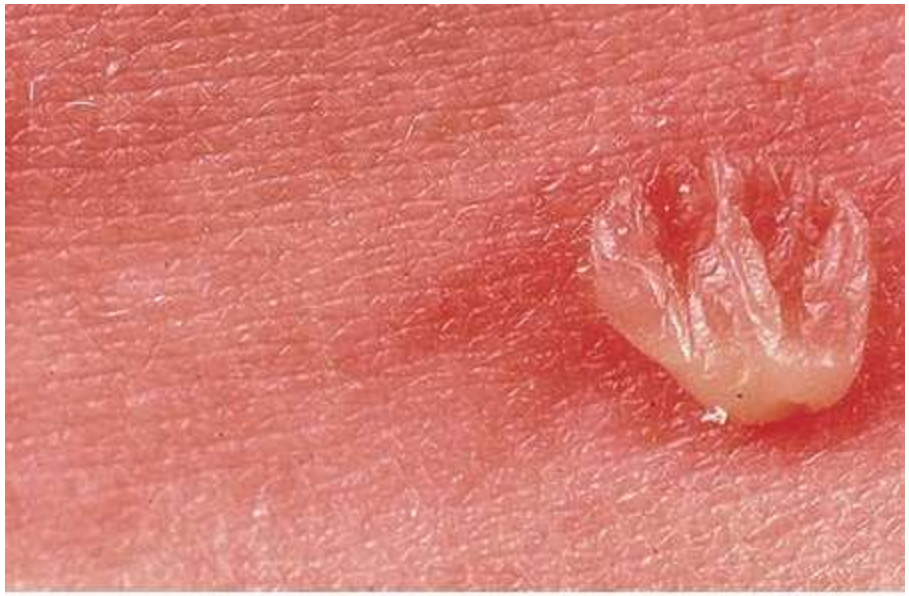
Antibodies against cell-surface or matrix antigens

- Type II response
- Immune hemolytic anemias (Rh disease as an example)
- Thrombotic thrombocytopenia purpura (Platelet integrin gpIIb/IIIa autoantigen)
- Goodpasture's syndrome (Non-collagenous domain of basement membrane collagen type IV as autoantigen)
- Myasthenia gravis as a result of antibody to acetylcholine receptor.
- Grave's disease of the thyroid as a result of antibody to thyroid stimulating hormone receptor.

Pemphigus vulgaris

- 80% of all cases
- 40-60 years of age
- No sex predilection
- Presents with multiple flaccid vesicles and bullae that rupture easily
- Begins in oral mucosa
- Scalp, face usual sites
- Chest, axillae, groin as other sites
- No pruritis
- Life threatening disease
- Responds to corticosteroids and immunosuppresion

Pemphigus vulgaris



This is the classic initial lesion:

Flaccid, easily ruptured vesicle or bulla on normal-appearing skin.

Ruptured vesicles lead to erosions that subsequently crust.

Fig. 6-9 Accessed 07/16/2010

Pemphigus vulgaris

- Histology
- Bulla forms above basal layer.
- Acantholysis as cells dissociated.
- Basal cells present as tombstones.
- Direct immunofluorescence to IgG (and C3) in the intercellular substance of the epidermis (desmoglein III)

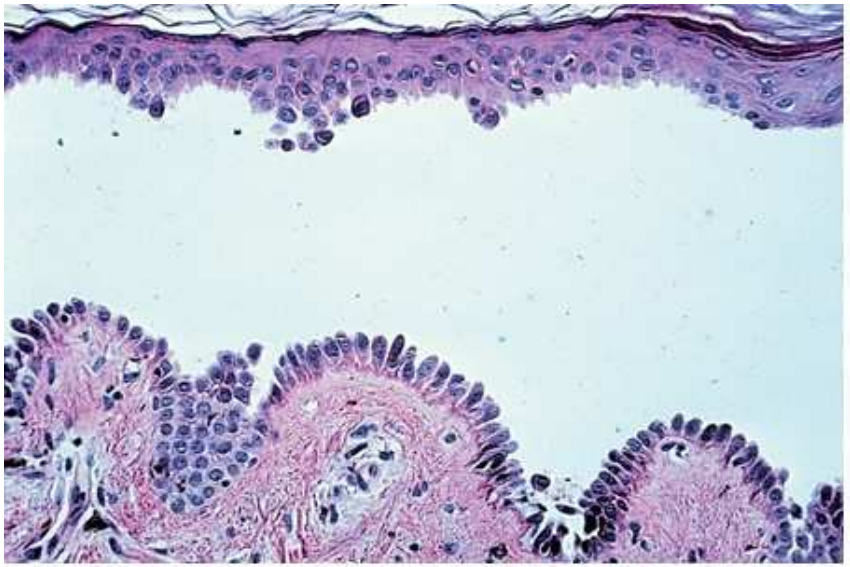


Fig. 52-7 Accessed 07/20/2010

Pemphigus vegetans

- Wart-like plaques.
- Groin, axilla, flexor surfaces.
- May evolve into Pemphigus vulgaris
- Antibody to desmoglein III.

Pemphigus erythematosus

- May resemble pemphigus foliaceus
- Malar area of face.
- Confined to seborrheic sites.
- Antibodies against both Dsg-1 and Dsg-3
- Associated with thymoma
- Associated with myasthenia gravis

Pemphigus antibody patterns

- Anti-Dsg (desmoglein)-1 antibodies in pemphigus foliaceus cause acantholysis only in the superficial epidermis of skin.
- In the deep epidermis and in mucous membranes, Dsg-3 compensates for antibody-induced loss of function of Dsg-1.
- In early pemphigus vulgaris, antibodies are present only against Dsg-3, which cause blisters only in the deep mucous membrane where Dsg 3 is present without compensatory Dsg-1.

Bullous pemphigoid

- 60-80 years-old
- No sex predilection
- Prodromal erythematous uriticarial lesion
- Evolves slowly then presents as a generalized eruption of serpiginous bullae
- Usual site are inner thighs and flexor surfaces
- Legs often first site manifest
- Occasionally oral or ocular involvement.
- May scar

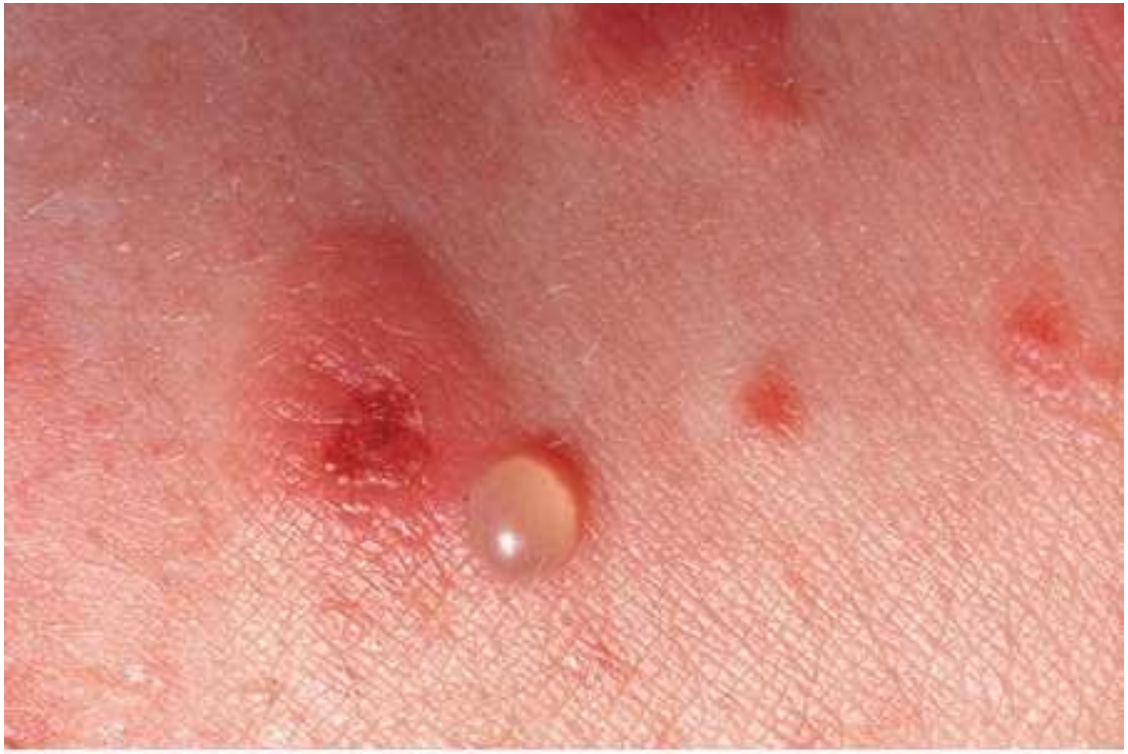
Bullous pemphigoid

- Histology
- Lysis at dermal-epidermal junction.
- Basal cell vacuolization.
- "Indian file" alignment of neutrophils at dermal-epidermal junction
- Perivascular infiltrate of neutrophils, lymphocytes, and eosinophils in papillary dermis

Bullous pemphigoid

- Antibodies to hemidesomosomes
- BPAg1 and BPAg2 or type XVII collagen
- Anti-laminin, if scarring
- Anti-BPAg 2 if ocular lesions or blister formation.
- Responds to topical steroids, tetracycline.

Bullous pemphigoid

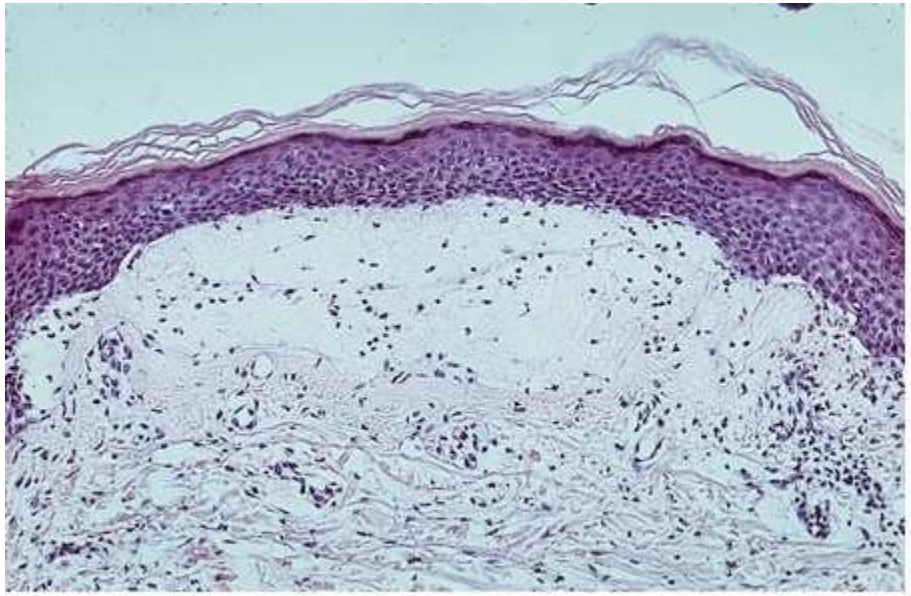


Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition:* http://www.accessmedicine.com

Urticarial plaques and a small, tense blister with a clear serous content.

Fig. 6-12 Accessed 07/16/2010

Bullous pemphigoid



Subepidermal (junctional) cleft formation and a perivascular and interstitial lymphoeosinophilic infiltrate are characteristic.

Linear deposits of IgG and C3 at the dermal-epidermal junction found in 80% of cases.

Fig. 6-8 Accessed 07/16/2010

Disease examples of Type III mechanisms

- Mixed essential cryoglobulinemia
- May be precipitated by Hepatitis C antigens
- Complex with non-specific immunoglobulin
- May precipitate in vessel walls at temperatures <37C
- Raynaud's phenomenon
- Palpable purpura
- Glomerulonephritis

Systemic lupus erythematosus

- Females 8:1 ratio
- Onset 30 years-old (females)
- Onset 40 years-old (males)
- More common in blacks
- 80% present with an erythematous, confluent, butterfly eruption over malar area
- May be photosensitive
- 80% will have aphthous ulcers arise in necrotic papular lesions in palate and oropharynx
- Symmetric small joint arthralgia and muscle pain in up to 90% of patients.

Systemic lupus erythematosus

- Anemia (of chronic disease or hemolysis) with leukopenia or thrombocytopenia.
- Nephritis occurs in half the patients.
- "Wire loop" pattern seen in glomerulus.
- May see Libman-Sacks endocarditis
- Sterile vegetations on both surfaces of cardiac valves
- Seizures.

Systemic lupus erythematosus

- 10% present with psoriaform lesions
- May see discrete papular or uriticarial lesions on face, arms, and dorsa of hands
- Hemorrhagic bullae during acute flares
- Pulmonary hypertension.
- Pleural effusion common in SLE.
- Low glucose and complement levels in fluid.

Table 6-11 Clinical and Pathologic Manifestations of Systemic Lupus Erythematosus

Clinical Manifestation	Prevalence in Patients (%)*
Hematologic	100
Arthritis, arthralgia or myalgia	80-90
Skin	85
Fever	55-85
Fatigue	80-100
Weight loss	60
Renal	50-70
Neuropsychiatric	25-35
Pleuritis	45
Pericarditis	25
Gastrointestinal	20
Raynaud phenomenon	15-40
Ocular	5-15
Peripheral neuropathy	15

*Percentages are approximate and may vary with age, ethnicity, and other factors. Table compiled with the assistance of Dr. Meenakshi Jolly, Rush Medical Center, Chicago.

Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-11 Accessed 12/10/2019

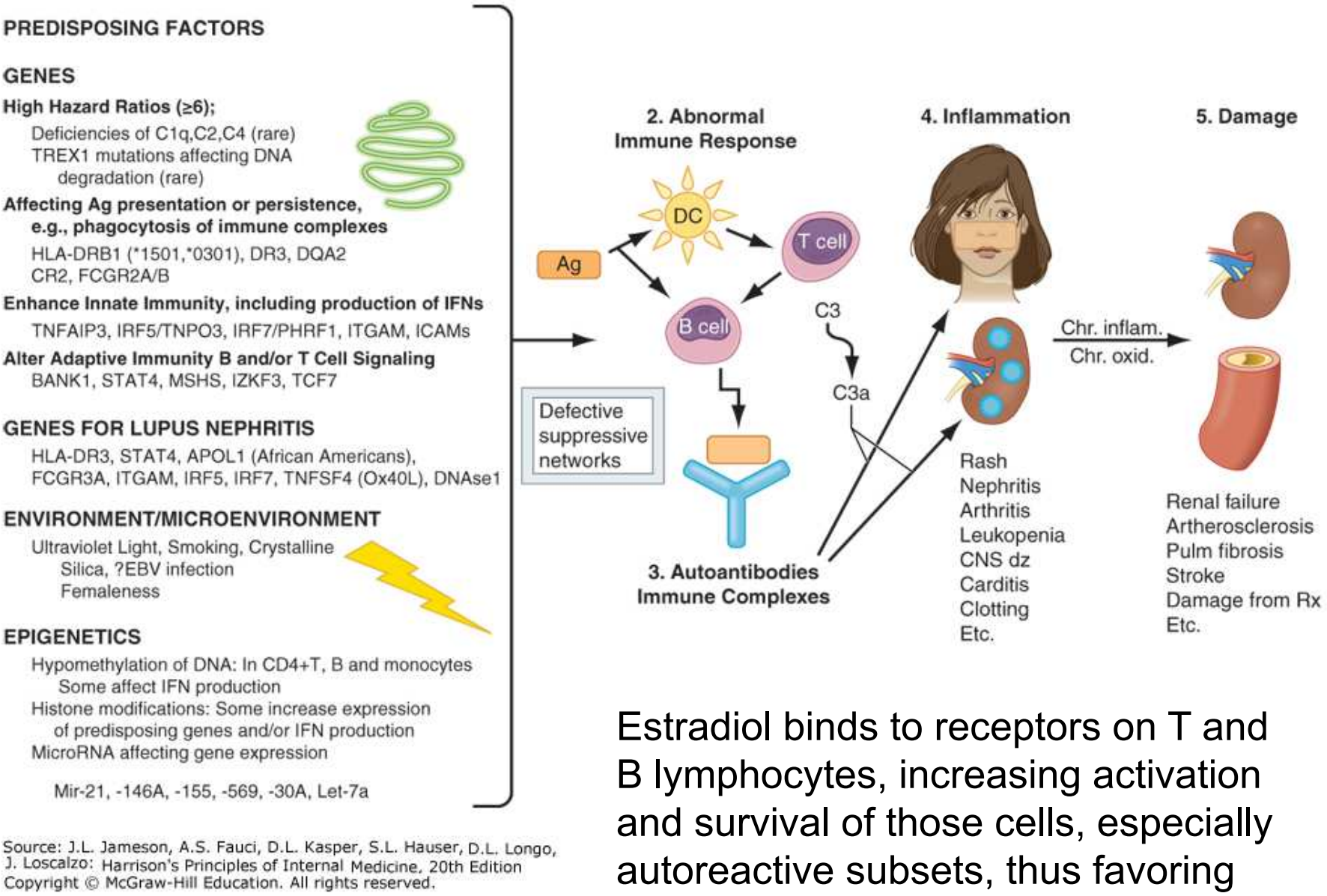
Table 6-9 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus*

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria >0.5 g/dL or >3 if quantitation not performed or Cellular casts—may be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance), or Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	Hemolytic anemia—with reticulocytosis, or Leukopenia—$<4.0 \times 10^9$ cells/L (4000 cells/mm^3) total on two or more occasions, or Lymphopenia—$<1.5 \times 10^9$ cells/L (1500 cells/mm^3) on two or more occasions, or Thrombocytopenia—$<100 \times 10^9$ cells/L (100×10^3 cells/mm^3) in the absence of offending drugs
10. Immunologic disorder	Anti-DNA antibody to native DNA in abnormal titer, or Anti-Sm—presence of antibody to Sm nuclear antigen, or Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test for lupus anticoagulant using a standard test, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by negative *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

*This classification, based on 11 criteria, was proposed for the purpose of identifying patients in clinical studies. A person is said to have SLE if any four or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

From Tan EM, et al: The revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271; and Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Table 6-9 Accessed 12/10/2019



Estradiol binds to receptors on T and B lymphocytes, increasing activation and survival of those cells, especially autoreactive subsets, thus favoring prolonged immune responses.

Antiphospholipid syndrome

- The antiphospholipid syndrome (primary)
- Characterized by
- Arterial and venous thrombosis
- Miscarriages
- Focal and ocular ischemia
- Present in 30-40% of patients with SLE (secondary antiphospholipid syndrome)
- VDRL falsely positive as is cardiolipin antibody
- Diluted Russell venom viper test to identify lupus anticoagulant

Clinical Features of Antiphospholipid Syndrome

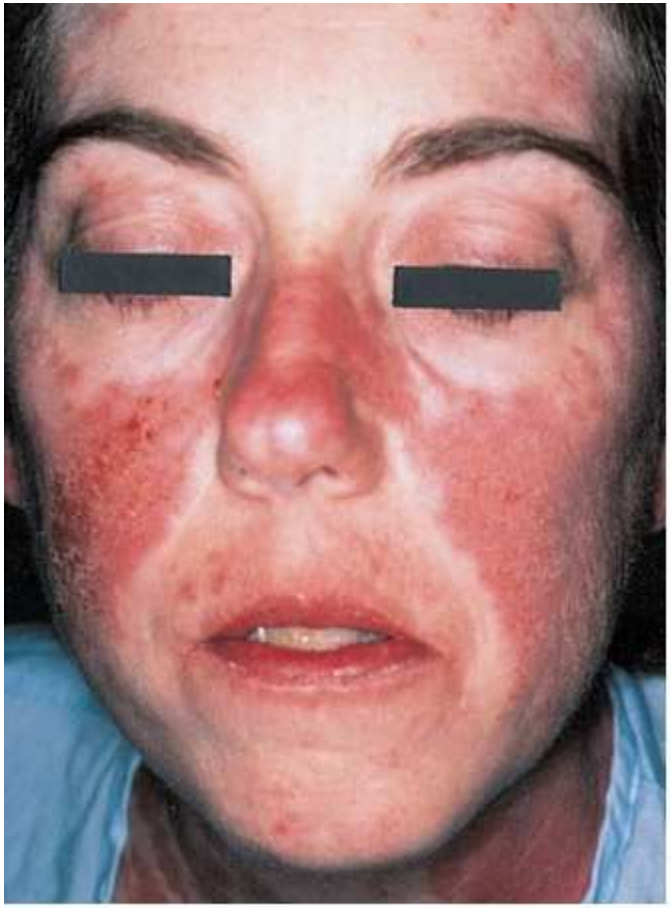
Manifestation	%
Venous Thrombosis and Related Consequences	
Deep vein thrombosis	39
Livedo reticularis	24
Pulmonary embolism	14
Superficial thrombophlebitis	12
Thrombosis in various other sites	11
Arterial Thrombosis and Related Consequences	
Stroke	20
Cardiac valve thickening/dysfunction and/or Libman-Sacks vegetations	14
Transient ischemic attack	11
Myocardial ischemia (infarction or angina) and coronary bypass graft thrombosis	10
Leg ulcers and/or digital gangrene	9
Arterial thrombosis in the extremities	7
Retinal artery thrombosis/amaurosis fugax	7
Ischemia of visceral organs or avascular necrosis of bone	6
Multi-infarct dementia	3
Neurologic Manifestations of Uncertain Etiology	
Migraine	20
Epilepsy	7
Chorea	1
Cerebellar ataxia	1
Transverse myelopathy	0.5
Renal Manifestations Due to Various Reasons (Renal Artery/Renal Vein/Glomerular Thrombosis, Fibrous Intima Hyperplasia)	3
Musculoskeletal Manifestations	
Arthralgias	39
Arthritis	27
Obstetric Manifestations (Referred to the Number of Pregnancies)	
Preeclampsia	10
Eclampsia	4
Fetal Manifestations (Referred to the Number of Pregnancies)	
Early fetal loss (<10 weeks)	35
Late fetal loss (≥10 weeks)	17
Premature birth among the live births	11
Hematologic Manifestations	
Thrombocytopenia	30
Autoimmune hemolytic anemia	10

Source: Adapted from R Cervera et al: Arthritis Rheum 46:1019, 2002.

Systemic lupus erythematosus

- 20% concordance in monozygotic twins
- 1-3% in dizygotic twins
- Speculative mechanisms
- STAT4 mutation
- mediates IL12 response to T-cell differentiation
- Failure of B and T_H self tolerance
- Toll like receptor engagement by RNA and DNA in immune complexes may activate B cells
- Promoted by Type I interferon
- BAFF (TNF family) promotes B cell survival
- UV light stimulates keratinocytes to produce IL1
- X chromosome related action

Systemic lupus erythematosus

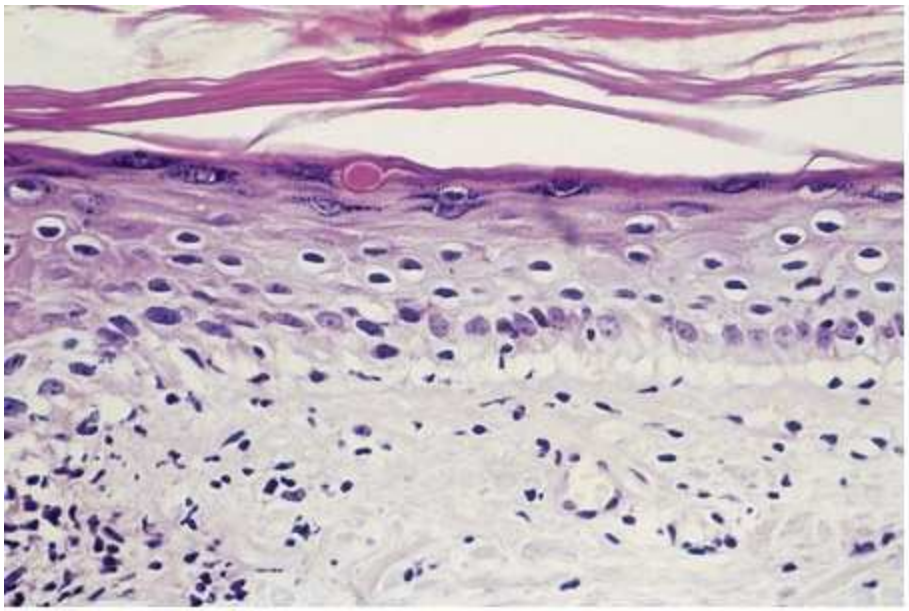


Characteristic malar ("butterfly") rash.

5 year survival is 93%

Fig. e10-60 Accessed 07/16/2010

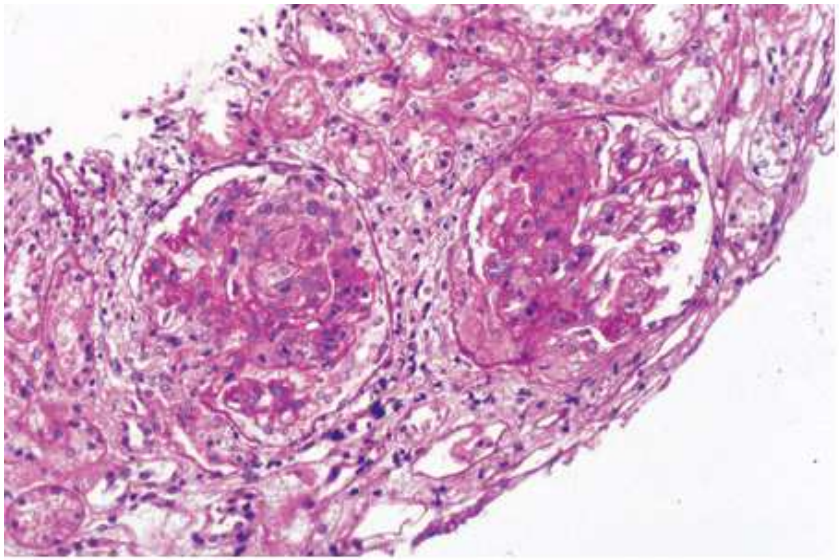
Lupus erythematosus



Hyperkeratosis, thinned epidermis devoid of rete ridges, and vacuolization of the basement membrane zone are present.

Fig. 6-11 Accessed 07/16/2010

Lupus nephritis



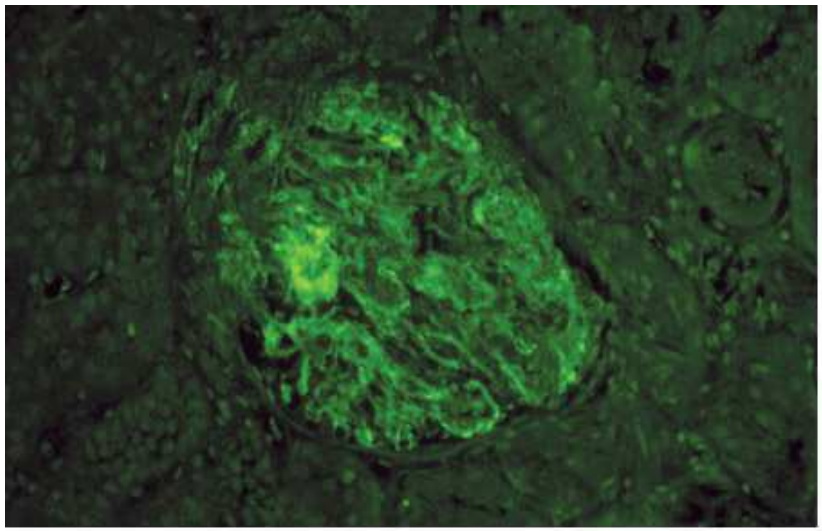
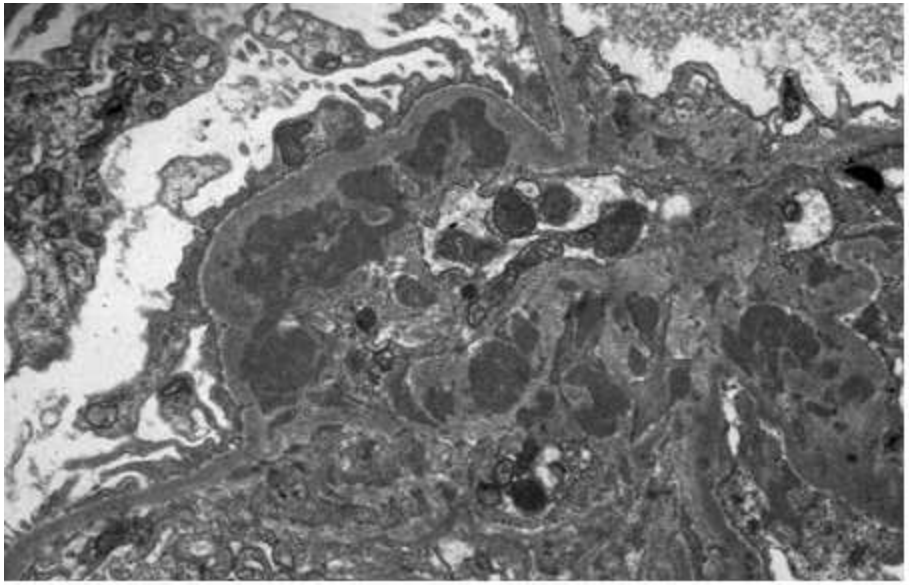


Fig. e9-10 Accessed 03/17/2010

Proliferative lupus nephritis manifests as endocapillary proliferation, which may result in segmental necrosis due to deposits, particularly in the subendothelial area (left).

Chunky irregular mesangial and capillary loop deposits are evident on immunofluorescence, with some of the peripheral loop deposits having a smooth, molded outer contour due to their subendothelial location. (right)

Lupus nephritis



Subendothelial, mesangial, and rare subepithelial dense immune complex deposits are evident, along with extensive foot process effacement in this electron micrograph.

(ABF/Vanderbilt Collection.) Fig. e9-10
Accessed 03/17/2010

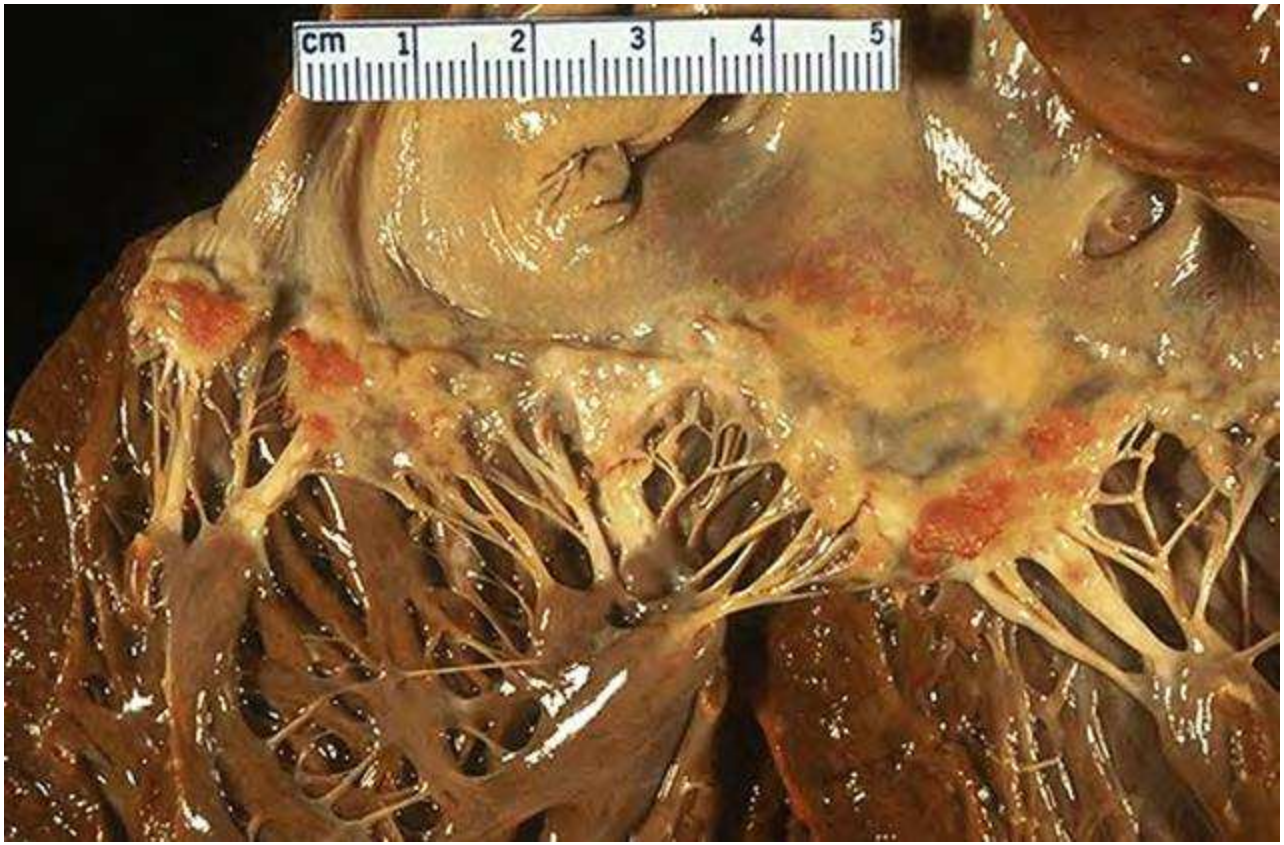
Classification of lupus nephritis

- Minimal mesangial (Class I)
- Minimal mesangial change on electron microscopy but not light microscopy
- Mesangial proliferative (Class II)
- Mesangial cell proliferation
- Focal (Class III)
- <50% glomeruli involved
- Increase in mesangial and endothelial cells

Classification of lupus nephritis

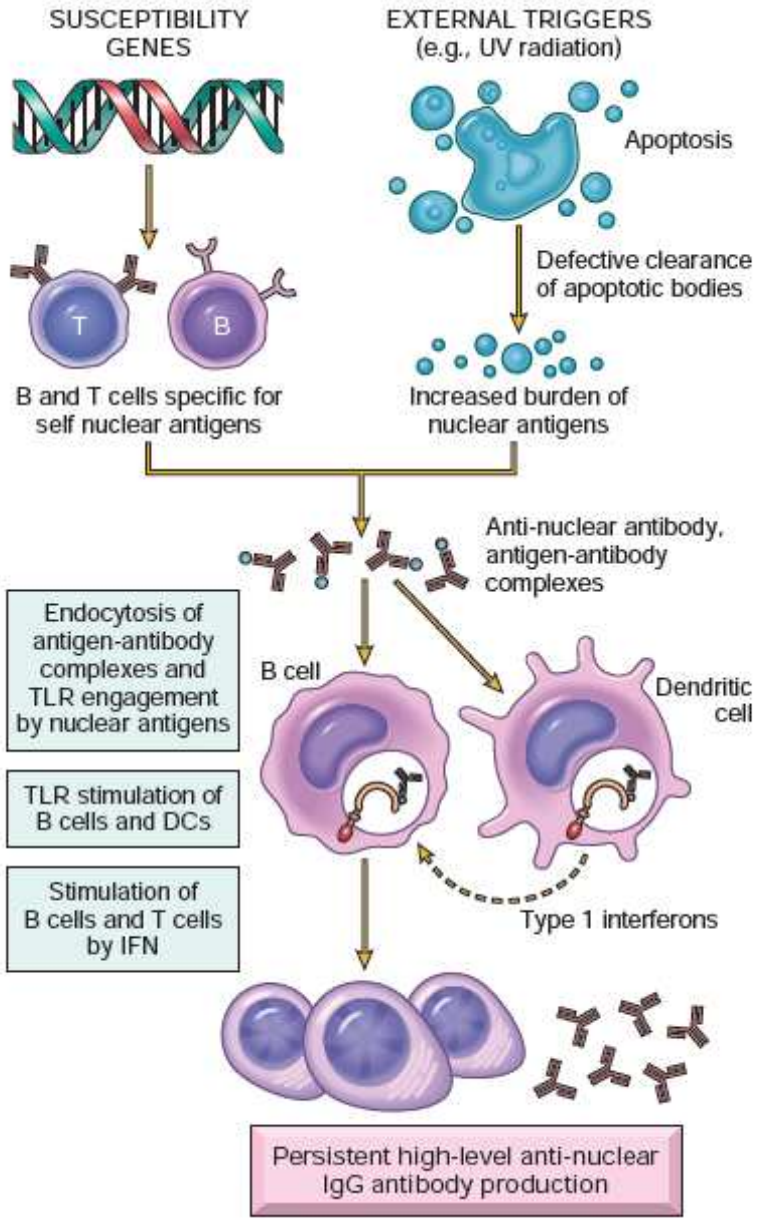
- Diffuse (Class IV)
- >50-90% glomeruli involved
- Diffuse changes
- Most commonly identified
- Membranous (Class V)
- Subepithelial immunocomplexes
- Increased deposition of basement membrane-like material
- Advanced sclerosing (Class VI)
- >90% glomeruli involved

Libman-Sacks endocarditis



Klatt, EC, Robbins and Cotran Color Atlas of Pathology. (2015) Elsevier. Philadelphia. Fig. 2-64Accessed 09/10/2019

Antinuclear antibody formation



Kumar, V, Abbas, AK, Aster, JC, “Diseases of the immune system,” in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig 6-25 Accessed 12/10/2019

ANA fluorescence patterns

- Not greatly utilized as direct antibody measurement in serum is now possible
- Antinuclear antibodies (ANA) are non-specific and polymorphic
- Usually important in high titer
- Patterns
- Homogeneous nuclear staining (histones)
- Rim of nucleus (dsDNA)
- Speckled nucleus (Sm, SSA, SSB)
- Nuclear discrete (RNA)
- Centromere (RNA)

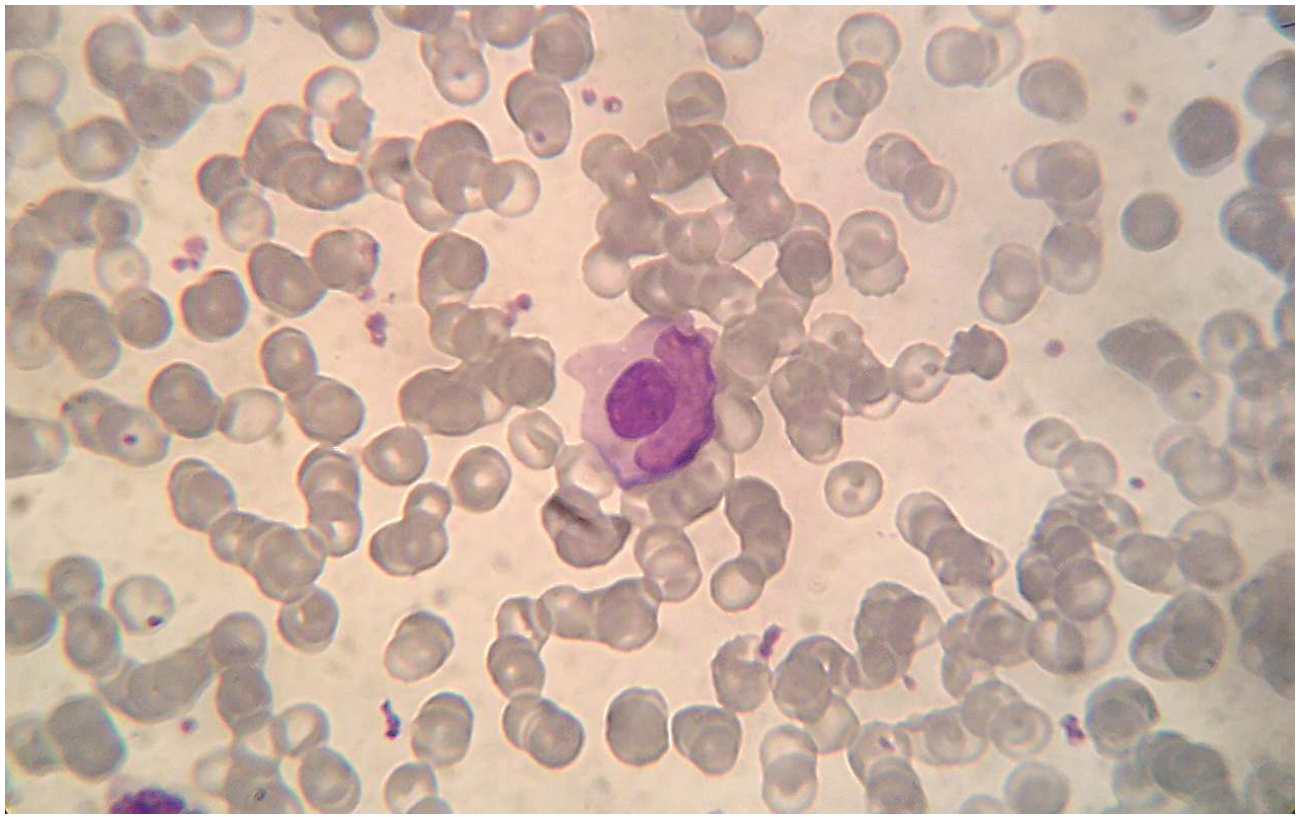
Systemic lupus erythematosus

- ANA is positive
- Polyclonal autoantibodies that react with nuclear proteins
- anti-dsDNA is positive (and diagnostic).
- Poor prognosis.
- anti-Sm is positive (and diagnostic)
- Has no prognostic value.
- Anti-Sm is more common in Africans and Asians than in whites.
- Elevated anti-Sm levels persist even after anti-DNA levels have returned to the normal range.
- Antiphospholipid antibodies may also be found

Systemic lupus erythematosus

- Anti-histone antibodies are found in drug induced disease
- Quinidine
- Chlorpromazine
- Hydralazine
- Isoniazid
- Methyldopa
- Procainamide
- Reversible disease if drug stopped.

LE cell



Monocyte that has phagocytized an apoptotic cell nucleus.

An old diagnostic test for systemic lupus erythematosus.

https://en.wikipedia.org/wiki/LE_cell#/media/File:LECell.jpg
Accessed 12/10/2019 Giemsa stain 45x

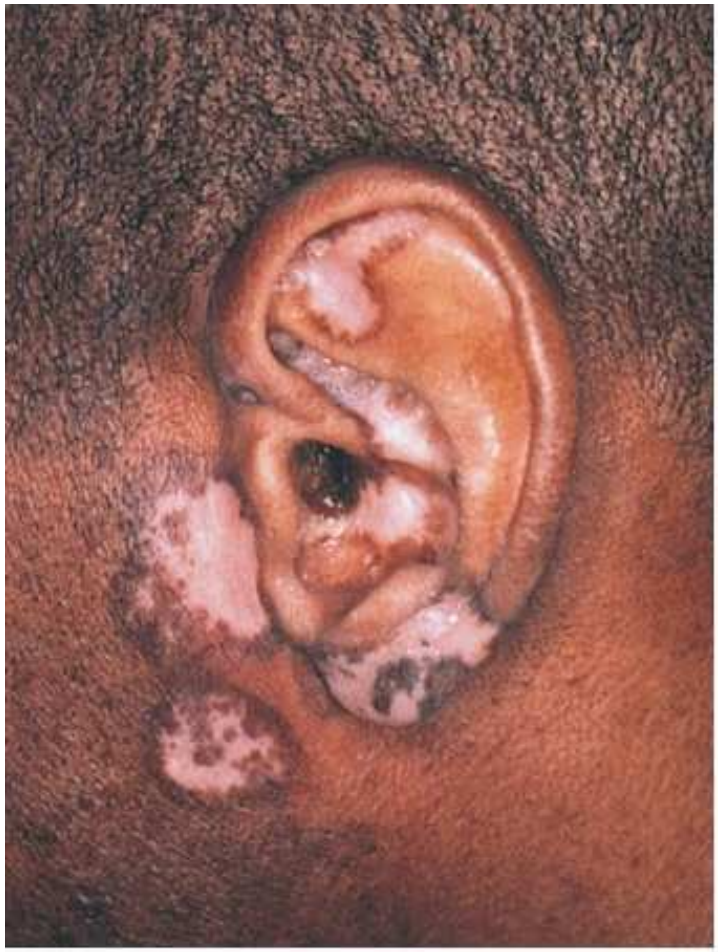
Systemic lupus erythematosus

- CNS or renal involvement excludes drug-induced SLE
- Patients with antibodies to Ro (SS-A), La, and RNP are at increased risk of having a child with SLE
- 40% of those mothers do not have SLE
- 1-2% of those infants manifest congenital heart block
- Childhood lupus is more common in boys than is adult lupus in men
- Renal disease twice that of adults
- Treatment initiated when organ damage threatened (NSAIDs, steroids, alkylating agents, anti-metabolites).

Chronic cutaneous (discoid) lupus erythematosus

- Violaceous, hyperpigmented, atrophic plaques
- Often with evidence of follicular plugging
- May result in scarring.
- Leave areas of depigmentation and white scars.
- If hair follicles destroyed, may lead to alopecia ("carpet tack").
- May be verrucoid.
- Face, head, neck.
- Rare on palms or soles.
- Uncommon for patients with cutaneous lupus erythematosus to have systemic disease.

Chronic cutaneous (discoid) lupus erythematosus



(Courtesy of Marilynne McKay, MD; with permission.)
Fig. e10-60 Accessed 07/16/2010

Systemic scleroderma

- Women 3:1
- Ages 30-50.
- Skin thickening of the extremities, face and trunk.
- Telangiectasias can be seen on face, palms, digits.
- Polyarthralgia and joint stiffness (synovitis)
- Raynaud phenomenon.
- Episodic attacks of vasospasm.
- Precipitated by cold, tobacco, stress.
- May lead to gangrene.
- Dilatation and impaired motility of lower esophagous as well as atony of the small bowel
- Fibrosis and muscular atrophy
- Pulmonary fibrosis and myocardial fibrosis.

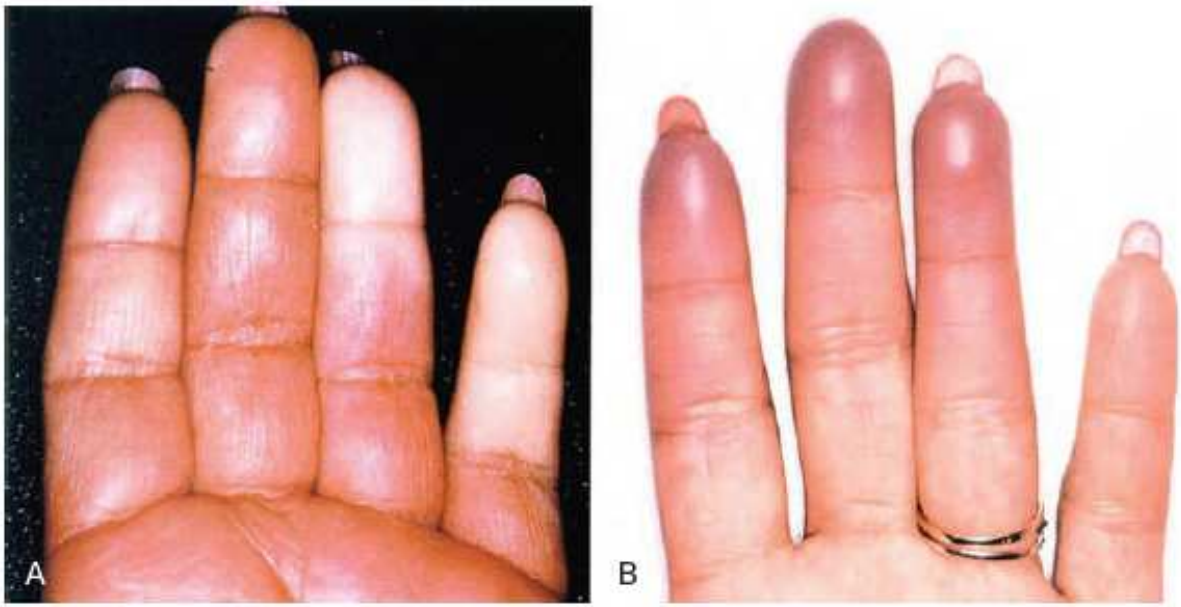


Figure 11-29 Raynaud phenomenon. **A,** Sharply demarcated pallor of the distal fingers resulting from spasm of the digital arteries. **B,** Cyanosis of the fingertips. (Reproduced from Salvarani C, et al: Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 347:261, 2002.)

Systemic scleroderma

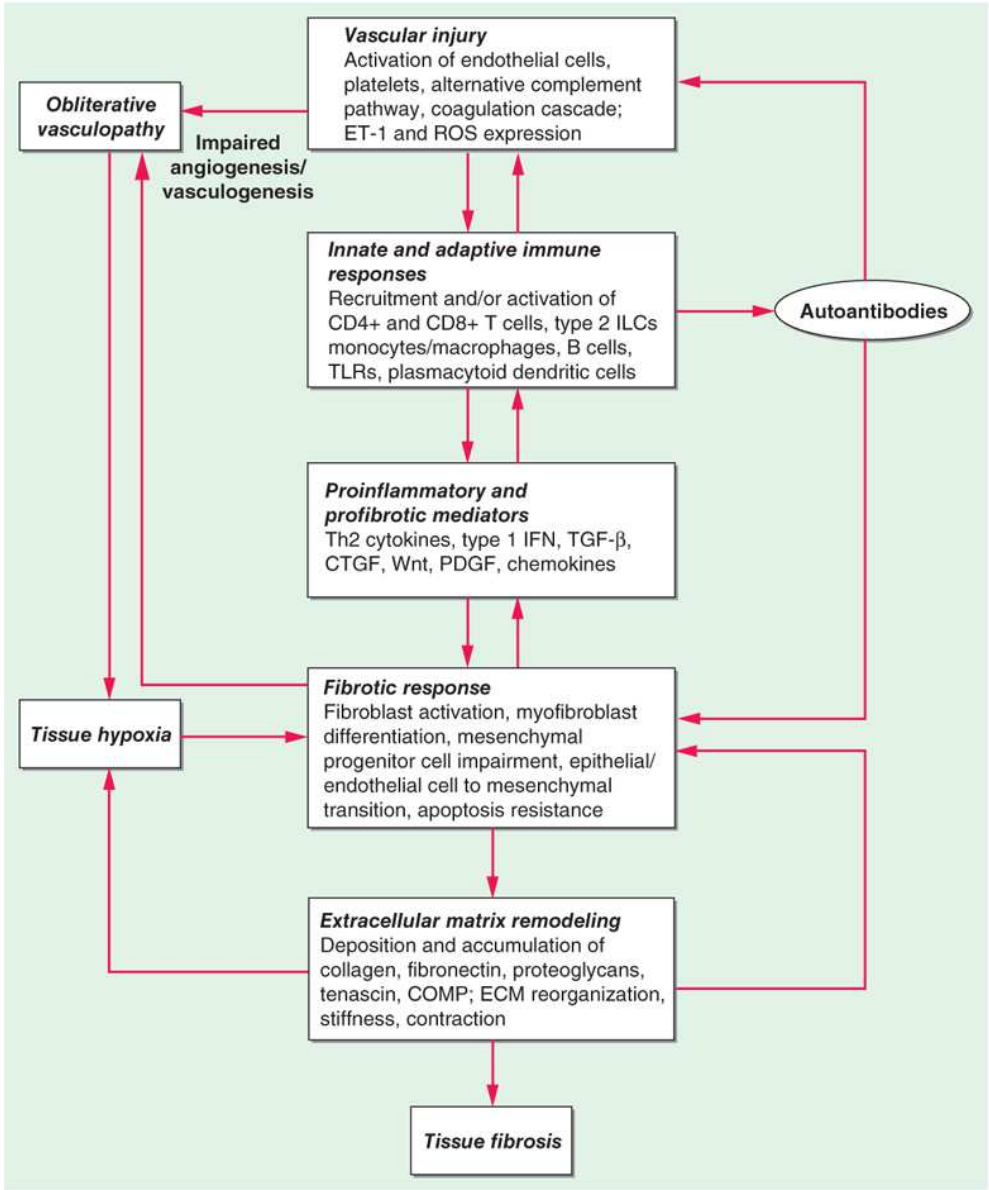
Medical Terms
80%-99% of people have these symp
Abnormality of the gastric mucosa
Arthralgia
Arthritis
Atypical scarring of skin
Autoimmunity
Chest pain
Chondrocalcinosis
Cough
Edema
Fatigue
Gastroparesis
Hyperkeratosis
Lack of skin elasticity
Myalgia
Nausea and vomiting
Skeletal muscle atrophy

30%-79% of people have these sym
Cachexia
Carious teeth
Gangrene
Malabsorption
Mucosal telangiectasiae
Myocardial fibrosis
Myositis
Papule
Pericarditis
Pulmonary fibrosis
Pulmonary infiltrates
Respiratory insufficiency
Skin ulcer
Telangiectasia of the skin
Xerostomia

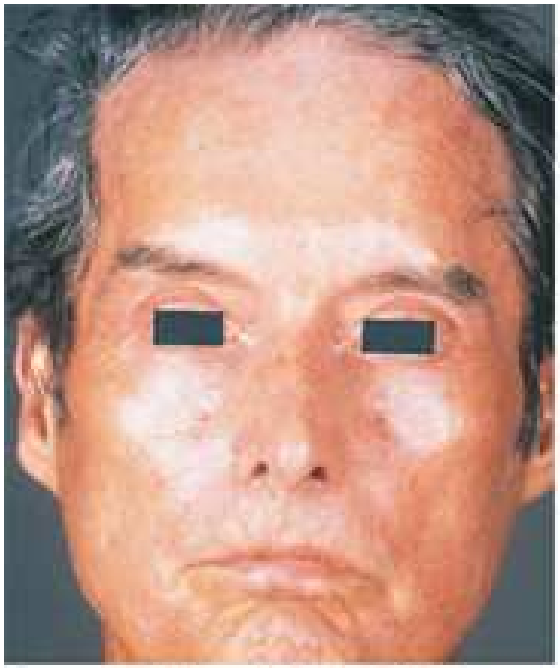
https://rarediseases.info.nih.gov/diseases/9748/systemic-scleroderma
Accessed 12/10/2019

Systemic scleroderma

- Infertility and amenorrhea are common.
- Diffuse disease is characterized by widespread skin involvement, rapid progression, and early visceral involvement
- Even sudden onset of malignant hypertension with rapidly progressive glomerulonephritis and renal failure
- Endothelial cell injury, fibroblast activation, and T-cells sensitized to collagen and other skin antigens perpetuate the disorder.
- Etiology unknown, however



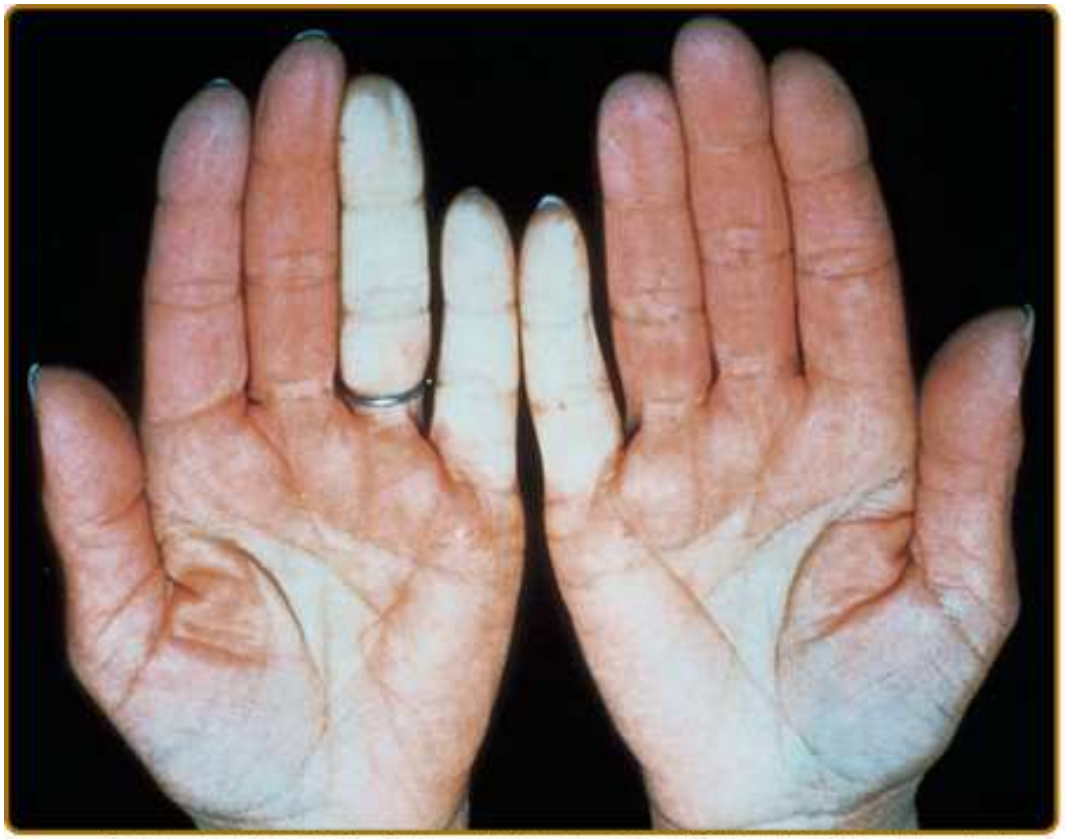
Systemic scleroderma



Characterized by typical expressionless, mask-like facies.

FIGURE 76e-62 Accessed 02/04/16

Raynaud phenomenon



Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

Ischemic phase of attack of Raynaud phenomenon.

Marked pallor of the ring and little fingers of the left hand and little finger of the right hand.

Fig. 170-1 Accessed 02/04/2016

Systemic scleroderma

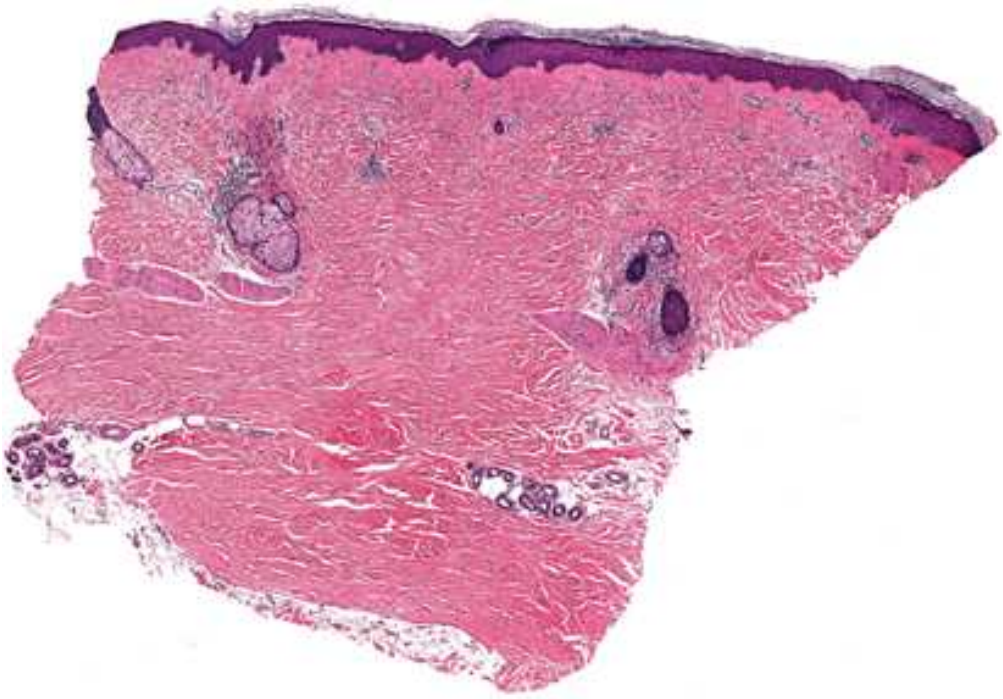


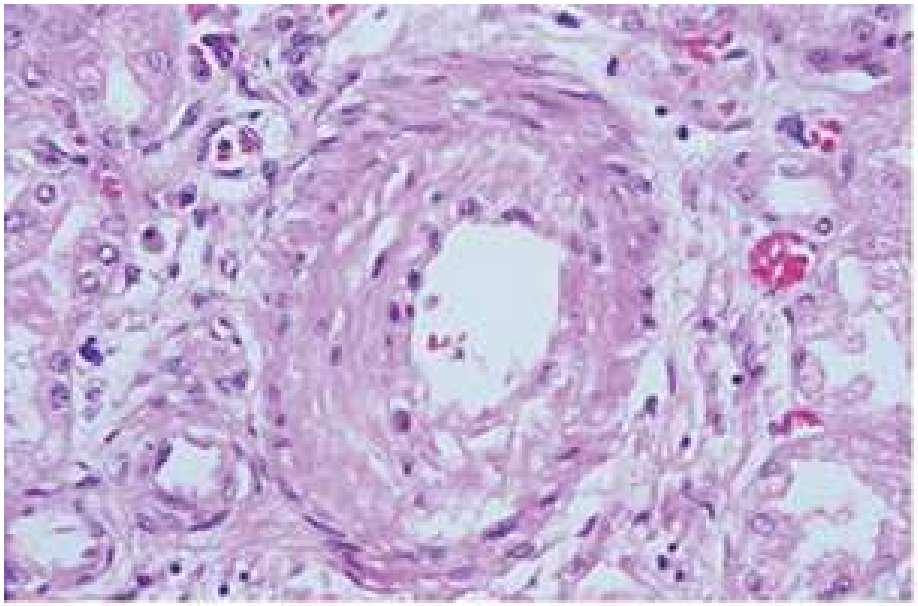
Fig. 20-38 Accessed 02/04/2016

The biopsy has a square morphology, which reflects the rigidity of the tissue biopsy specimen due to striking pan-dermal sclerosis.

The fibrosing reaction extends into the panniculus. The number of adnexal structures is reduced.

A significant inflammatory cell infiltrate is not observed. This is in contradistinction to morphea, … ..hich a prominent inflammatory cell infiltrate is present.

Systemic scleroderma



C

Fig. 382-2C Accessed 02/04/2016

Medial fibrosis and smooth muscle arteriolar hyperplasia in the kidney.

Diffuse alveolar septal fibrosis and chronic inflammatory cell infiltrates develop as well in the lung.

Pulmonary hypertension develops over time.

Systemic scleroderma

- Anti-topoisomerase antibodies (anti-Scl-70) found. Usually associated with pulmonary fibrosis and peripheral vascular disease.
- Inflammatory. T_{H2} cells found in skin. Microvascular disease consistently present.
- Elevated erythrocyte sedimentation rate.
- Anemia of chronic disease.
- 20% 10 year survival.
- ACE inhibitors to treat hypertension.
- Calcium channel blockers to treat Reynaud's phenomenon.
- Corticosteroids to treat fibrosis, cyclophosphamide to treat alveolitis.

CREST syndrome

- **C**alcinosis
- **R**aynaud
- **E**sophageal dysmotility
- **S**clerodactyly
- **T**elangiectasia
- Limited cutaneous sclerosis
- Appear years after onset of Raynaud's phenomenon.

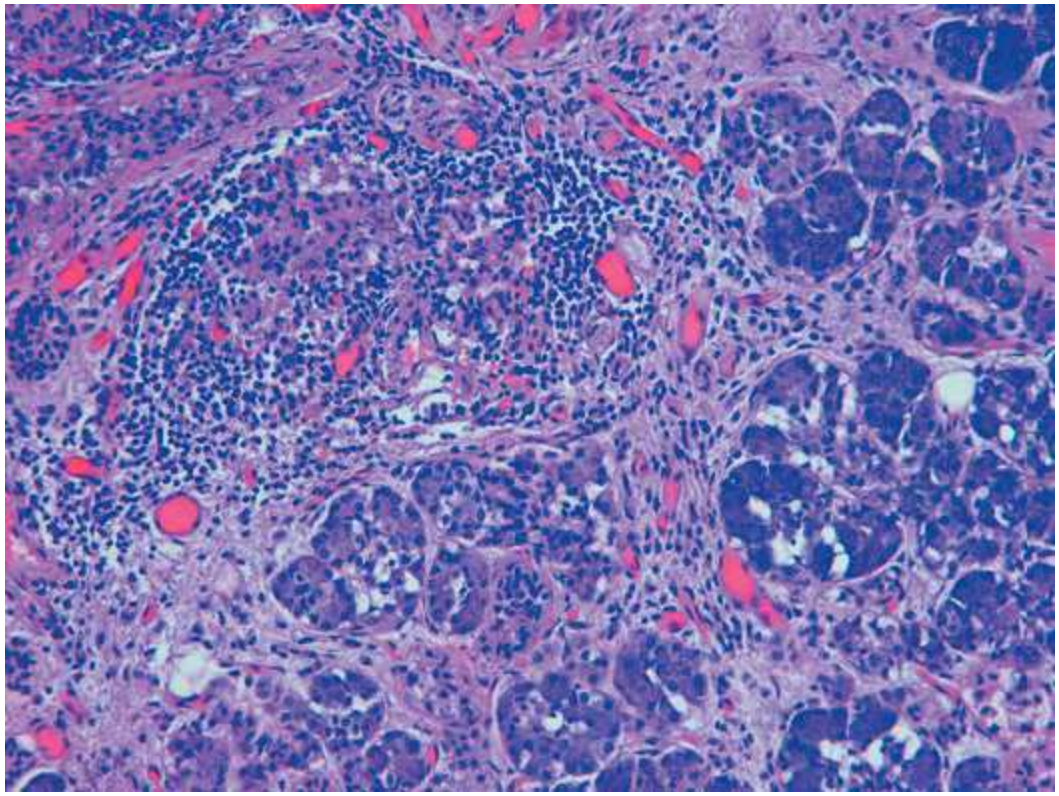
CREST syndrome

- **C**alcinosis
- **R**aynaud
- **E**sophageal dysmotility
- **S**clerodactyly
- **T**elangiectasia
- Limited cutaneous sclerosis
- Appear years after onset of Raynaud's phenomenon.

Sjögren's syndrome

- Second most common rheumatologic disorder.
- Much more common in women, ages 50-60 years old.
- May occur as primary disease or secondary to other autoimmune disorders.
- Activated lymphocytes accumulate around blood vessels in ducts, particularly in salivary and lacrimal glands. Target the muscarinic acetylcholine receptor. (Mikulicz syndrome).
- Dry mouth and dry eyes. (Sicca syndrome)
- May have chronic arthritis.
- Biopsy of minor salivary gland diagnostic.

Sjögren's syndrome



Low-power photomicrograph of a minor salivary gland lobule showing multiple lymphocytic foci that are replacing the acinar structures.

Periductal and perivascular inflammation. CD4+ cells predominate.

Ductular lining cells proliferate, may obstruct. (H&E, 40 X).

Figure 3-4
Kemp, WL, Burns, DK, Brown, TG, The Big Picture. McGraw-Hill. New York. 2008 Accessed 02/03/2016

Diagnostic criteria

- 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR)
- 1. Anti-Ro/SSA Positive (3 points)
- 2. Lip Biopsy with Focus > 1 foci/4mm^2 (3 points)
- 3. Ocular Staining Score ≥ 5 or Van Bijsterveld Score ≥ 4 (1 point)
- 4. Schirmer's Test ≤ 5mm/5min (1 point)
- 5. Unstimulated Salivary Flow Rate ≤ 0.1 mL/min (1 point)
- Diagnosis if >4 points

Sjögren's syndrome

- 75% rheumatoid factor positive
- 90% ANA positive
- Anti-Ro (antibody to the leading single strand of DNA, ssA) and anti-La (antibody to the lagging single strand of DNA, ssB) are associated with earlier onset, longer duration, and extra-glandular manifestations.
- Risk for lymphoma.
- The Schirmer test evaluates tear production.
- Rose Bengal dye may be used to view damaged corneal epithelium.
- Supportive therapy (artificial tears, gum chewing to promote salivation) unless extra-glandular manifestations present.

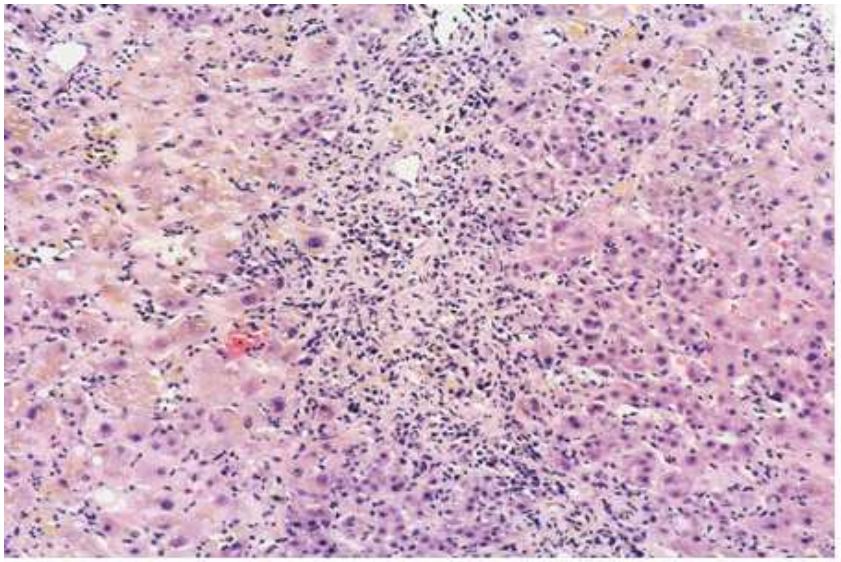
Autoimmune hepatitis

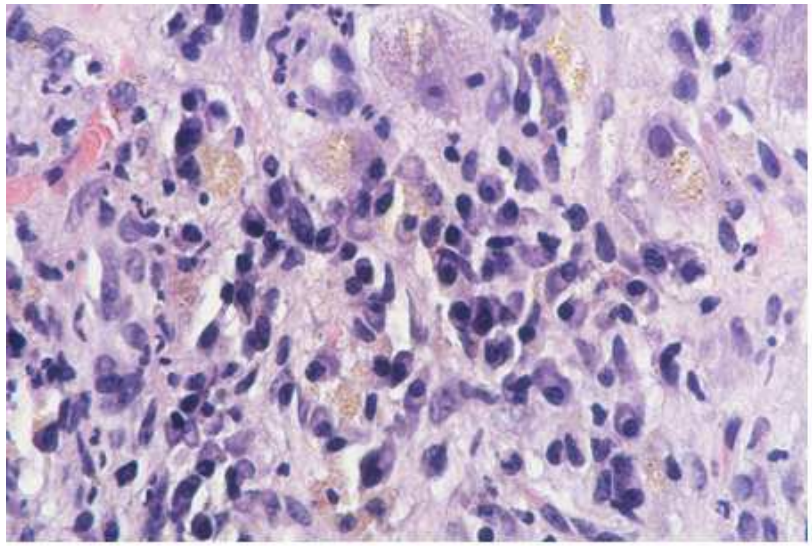
- Type I
- Seventy-eight percent (78%) occur in middle-aged women.
- Viral hepatitis must be excluded.
- Serum IgG elevated.
- Positive ANA, anti-smooth muscle actin antibody, anti-soluble liver antigen/liver-pancreas antigen, and, less commonly, anti-mitochondrial antibody.
- Associated with HLA-DR3.
- May be associated with Grave's disease, Hashimoto's thyroiditis.

Autoimmune hepatitis

- Type II
- Occurs in children and teenagers
- Positive anti-liver kidney microsome-1 (ALKM-1) antibodies (largely against CYP2D6) and anti-liver cytosol (ALC-1) in Kidney involved as well.
- Both Types I and II may occur acutely (40%).
- Mortality rate is 40% within 6 months if untreated. Cirrhosis in 40% of survivors.
- Both Types I and II respond to prednisone and azathioprine (80%).
- May use budenoside instead of prednisone in non-cirrhotics.
- Liver transplantation may be necessary.

Autoimmune hepatitis





Portal inflammation and erosion of the limiting plate of periportal hepatocytes by infiltrating lymphocytes and plasma cells. (H&E, 10x,20x)

Figs. e26-9 and e26-10
Accessed 03/01/2010

Primary biliary cirrhosis

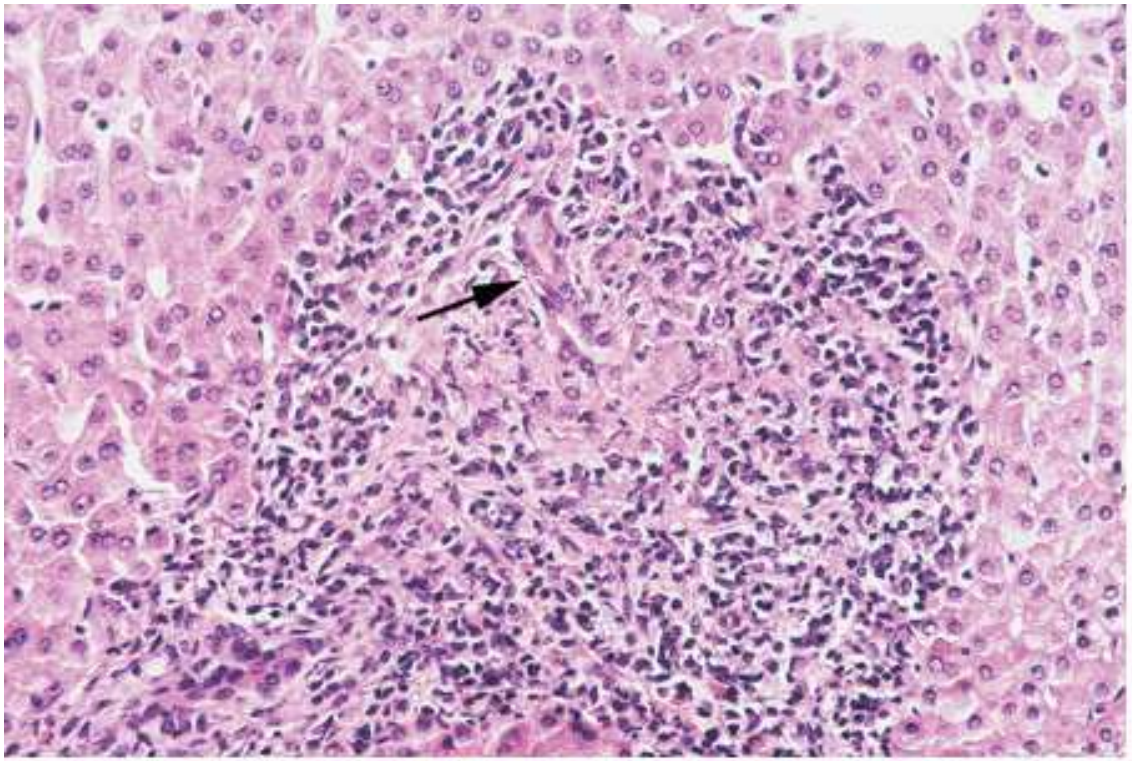
- Occurs in middle aged women (90%).
- Insidious onset with fatigue and pruritis of unknown etiology.
- Painful hepatomegaly.
- Up to 40% may have skin hyperpigmentation
- Melanin deposition
- 40-70% have an inflammatory arthropathy.
- Lid xanthelasma a late finding.

Primary biliary cirrhosis

- Association with Sjögren's disease.
- Autoimmune disorder.
- 90% anti-mitochondrial antibodies
- To the E2 component of the pyruvate dehydrogenase complex on the mitochondrial membrane
- Respond to immunosuppression.
- Cholestasis prominent. Rise in bilirubin suggests incipient hepatic decompensation.
- Cirrhosis and liver cancer risks greatly increased.
- Transplantation associated with 10-year survivals of 70%.

Primary biliary cirrhosis

- Characteristic proliferation of bile ducts (arrow) with associated lymphocytic infiltrate in the portal triad is shown in the photo



Figs. e26-11
Accessed 03/01/2010

Table 11-3 Primary Forms of Vasculitis

	Giant Cell Arteritis	Granulomatosis with Polyangiitis	Churg-Strauss Syndrome	Polyarteritis Nodosa	Leukocytoclastic Vasculitis	Buerger Disease	Behçet Disease
Sites of Involvement							
Aorta	+	–	–	–	–	–	–
Medium-sized arteries	+	+	+	+	–	+	+
Small-sized arteries	–	+	+	+	+	+	+
Capillaries	–	–	–	–	+	–	+
Veins	–	–	–	–	+	+	+
Inflammatory Cells Present							
Lymphocytes	+	+	+	±	±	±	±
Macrophages	+	+	+	±	±	±	±
Neutrophils	Rare	+	+	±	±	±	Required
Eosinophils	Very rare	±	Required	±	±	±	±
Other Features							
Granulomas	± *	Required *	±	–	–	–	–
Giant cells	Often; not required	±	–	–	–	–	–
Thrombosis	±	±	±	±	±	Required	±
Serum ANCA positivity	–	+	+	±	–	–	–
Clinical history	>40 y years old, ± polymyalgia rheumatica	Any	Asthma, atopy	Any	Any	Young male smoker	Orogenital ulcers

*The granulomas of giant cell arteritis are found within the vessel wall as part of the inflammation comprising the vasculitis, but need not be present to render the diagnosis. The granulomas of granulomatosis with polyangiitis are larger, spanning between vessels, and associated with areas of tissue necrosis.

From Seidman MA, Mitchell RN: Surgical pathology of small-and medium-sized vessels. In Current Concepts in Cardiovascular Pathology, Philadelphia, Saunders, 2012.

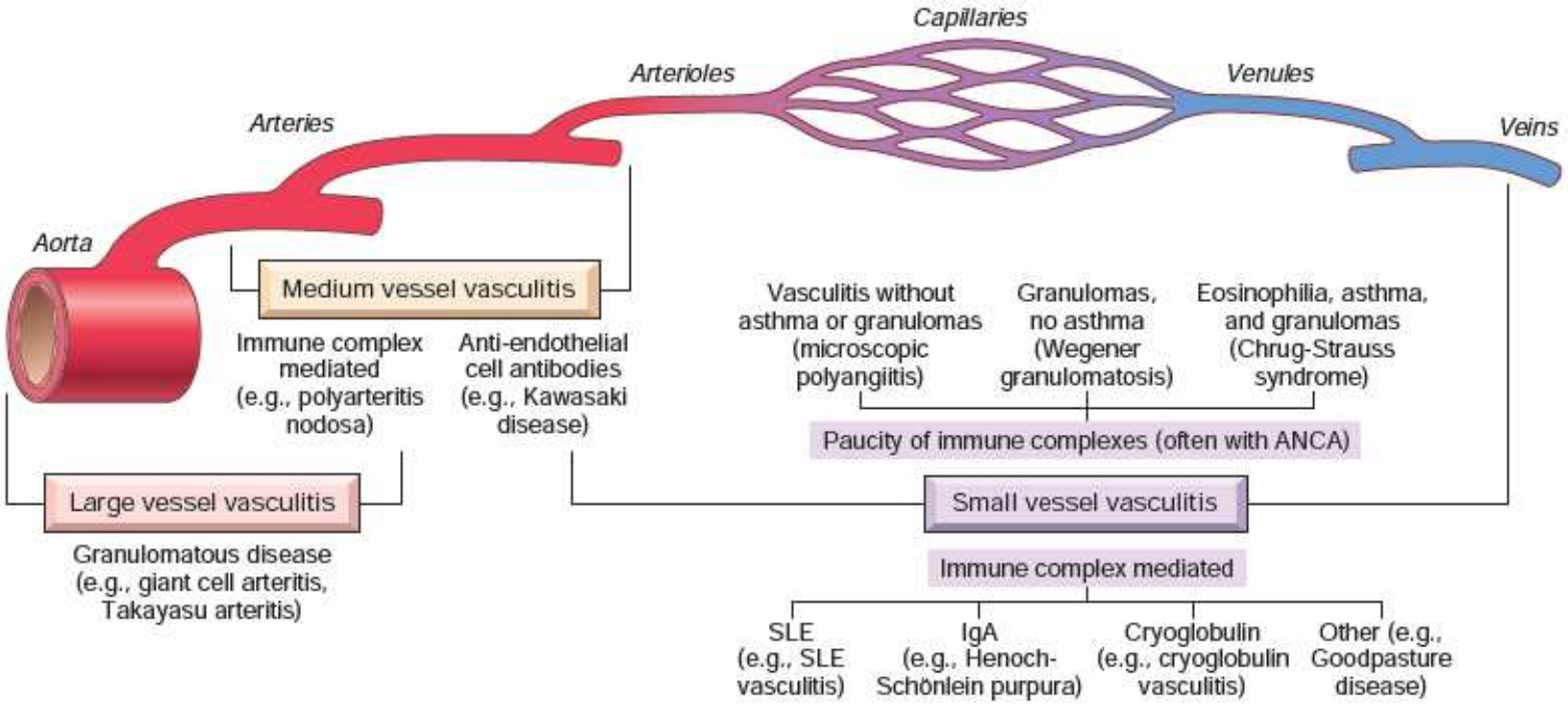


Figure 11-23 Vascular sites typically involved with the more common forms of vasculitis, as well as their presumptive etiologies. Note that there is a substantial overlap in distributions. ANCA, Antineutrophil cytoplasmic antibody; SLE, systemic lupus erythematosus.

Vasculitides

- Small Vessel Disease
- Granulomatosis with polyangiitis (Wegner's)
- Microscopic polyangiitis (MPO-ANCA)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Medium Vessel Disease
- Polyarteritis nodosa (without granulomata)
- Kawasaki's arteritis (anti-endothelial cell antibodies)
- Large Vessel Disease
- Giant cell arteritis (with granulomata)
- Takayasu's arteritis (with granulomata)

Granulomatosis with polyangitis

- Once known as Wegner's granulomatosis
- 90% Upper respiratory tract involvement (nose)
- 95% Lower respiratory tract involvement (lungs)
- 80% Renal involvement (crescentric in glomerulus)
- Hematuria with red cell casts
- Skin involvement.
- May also see uveitis.
- Men
- 40-50 years of age

Granulomatosis with polyangitis

- Necrotizing granulomatous inflammation of small and medium sized arteries
- 95%, antibodies to PR3-ANCA and MPO-ANCA
- Corticosteroids and cyclophosphamide therapy.
- Mortality 100% if untreated.

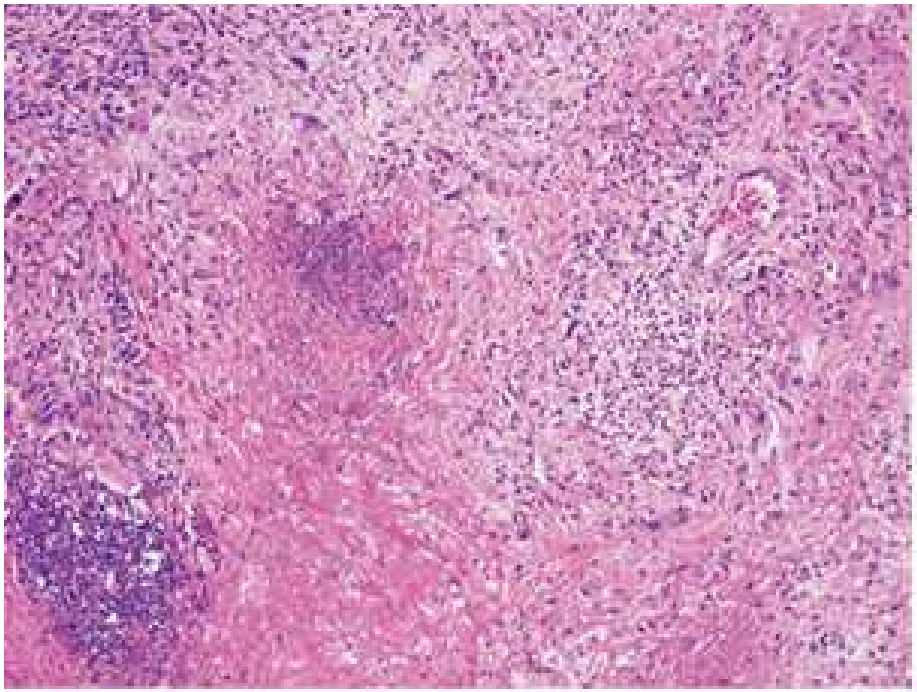
Anti-neutrophil cytoplasmic antibodies

- Antibodies to cellular constituents
- Do not form circulating immune complexes
- Not found in vascular lesions ("pauci-immune")
- Anti-proteinase-3 ANCA (PR3-ANCA)
- Was once known as c-ANCA
- Shares homology with microbial peptides
- Anti-myeloperoxidase ANCA (MPO-ANCA)
- Was once known as p-ANCA
- Myeloperoxidase is a lysozomal granule associated with free radical formation
- May be generated by drug (propothiouracil)

Anti-neutrophil cytoplasmic antibodies

- Non PR3 and MPO ANCAs may be seen in other disorders that do not present as vasculitis
- Inflammatory bowel disease
- Sclerosing cholangitis
- Rheumatoid arthritis
- All are upregulated by TNF
- Activated neutrophils lead to tissue damage

Granulomatosis with polyangitis



Courtesy of William D. Travis, MD; with permission.
Figure 385-2 Accessed 02/04/2016

- This area of geographic necrosis has a serpiginous border of histiocytes and giant cells surrounding a central necrotic zone.
- Vasculitis is also present with neutrophils and lymphocytes infiltrating the wall of a small arteriole (upper right).

Eosinophil granulomatosis with polyangitis (EGPA)

- Once known as Churg-Strauss Syndrome)
- Presents with nasal polyps or rhinitis
- Asthma is a distinguishing feature
- Progresses to eosinophilia
- Vasculitis develops.
- Mononeuritis multiplex
- Shooting pains and muscle weakness in hands and feet with wrist or foot drop
- 1/3 have pulmonary infiltrates (transient)
- The arteriolar biopsy contains granulomas.
- MPO-ANCA positive.

Limited granulomatosis with polyangiitis

- More common in males
- >45 years of age
- Limited granulomatosis does not involve kidney
- Rarely associated with diffuse pulmonary hemorrhage
- Waxing and waning of pulmonary nodules and infiltrates on chest x-ray is relatively specific

Limited granulomatosis with polyangiitis

- PR3-ANCA positive: diffuse cytoplasmic staining directed against neutrophil serine proteinase 3
- 90% positive in active generalized disease
- 60% positive in limited disease
- MPO-ANCA directed against myeloperoxidase is negative
- If positive, is polyarteritis or crescentic glomerulonephritis

Microscopic polyangitis

- Most common signs at presentation:
- 80% glomerulonephritis
- 70% weight loss
- 60% skin lesions (palpable purpura in dependent areas; splinter hemorrhages)
- 60% nerve damage (mononeuritis multiplex)
- 55% fever
- 12% pulmonary hemorrhage
- Small vessel disease.
- Biopsy does not show granulomas in the arterioles.
- MPO-ANCA positive.
- HBV negative.

Microscopic polyangitis

A blood vessel within the muscle shows an intense inflammatory infiltrate with destruction of the blood vessel wall, confirming the diagnosis of vasculitis.

https://www.hopkinsvasculitis.org/types-vasculitis/microscopic-polyangiitis/ Accessed 02/20/2020

Polyarteritis nodosa

- Men predominate
- Ages 45-65
- Small and medium arteries involved
- Ischemia or infarction of organ
- Commonly involves intestinal tract, heart, eye
- May present with livedo reticularis or palpable purpura
- Mononeuritis multiplex develops
- 50% of those with renal involvement are hypertensive

Polyarteritis nodosa

- Immune complex disease
- 30% precipitated by Hepatitis B
- Also implicated are
- Hepatitis C
- Parvovirus B19
- Group A Streptococcus
- CECR1 mutation in cutaneous form
- Deficiency of ADA2 protein (adenosine deaminase)
- Essential for endothelial and neutrophil development
- 80% 5-year and 67% 10-year survival

Clinical Manifestations Related to Organ System Involvement in Polyarteritis Nodosa

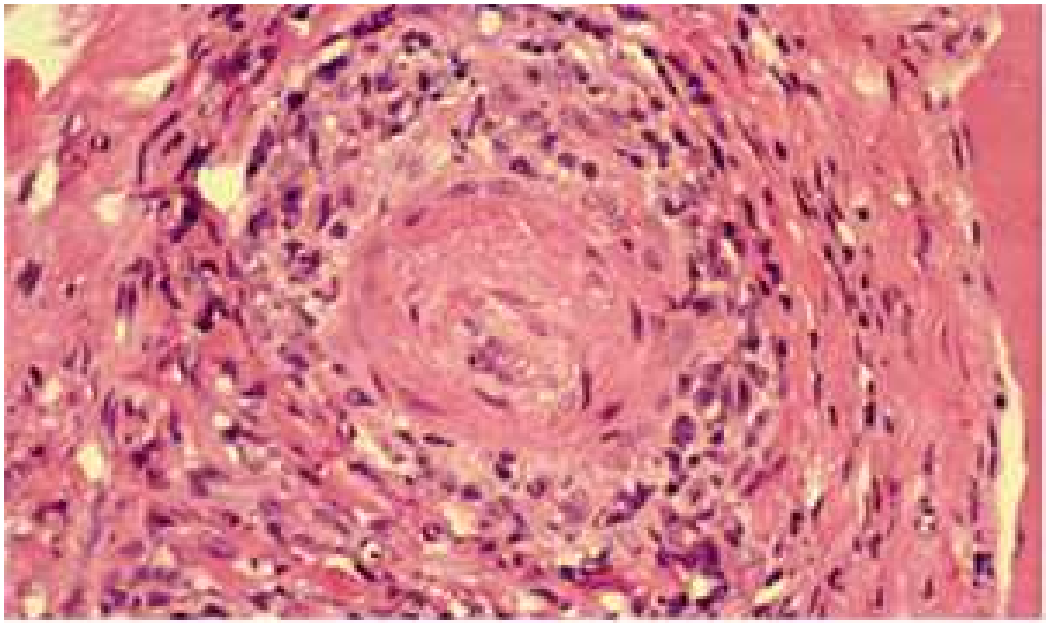
Organ System	Percent Incidence	Clinical Manifestations
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy, mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting, bleeding, bowel infarction and perforation, cholecystitis, hepatic infarction, pancreatic infarction
Skin	43	Rash, purpura, nodules, cutaneous infarcts, livedo reticularis, Raynaud's phenomenon
Cardiac	36	Congestive heart failure, myocardial infarction, pericarditis
Genitourinary	25	Testicular, ovarian, or epididymal pain
Central nervous system	23	Cerebral vascular accident, altered mental status, seizure

Source: From TR Cupps, AS Fauci: *The Vasculitides.* Philadelphia, Saunders, 1981.

Polyarteritis nodosa

- Clinical manifestations result from ischemia and infarction of affected tissues and organs.
- The course is frequently remitting and episodic
- Histopathology:
- Transmural inflammation of the arterial wall with a mixed infiltrate of neutrophils, eosinophils, and mononuclear cells, frequently accompanied by fibrinoid necrosis.
- Luminal thrombosis can occur.
- May develop micro-aneurysms

Polyarteritis nodosa



From a sural nerve biopsy in a patient with Polyarteritis nodosa, who had presented with a mononeuritis multiplex.

Neutrophils are seen infiltrating all layers of this medium-sized vessel, which resulted in vessel occlusion and nerve infarction.

Figure 386e-19 Accessed 02/04/2016

Kawasaki disease

- 80% <4 years of age
- Presents with high fever, conjunctival infection, strawberry tongue, and rash with desquamation of the palms and soles.
- Coronary vasculitis with thrombosis develops.
- May also see coronary artery aneurysms
- Medium vessel disease.
- Dense transmural infiltrate of arterial wall.
- Anti-endothelial cell antibodies
- High dose intravenous immunoglobulins and aspirin are effective. One of the indications of aspirin use in children.

Giant cell arteritis

- Most common cause of vasculitis in adults >50 years of age
- Average age of onset is 72 years of age
- Women (3:2)
- More common in those of Scandinavian origin
- Large vessel disease
- Predilection for temporal arteries (temporal arteritis)
- May involve ophthalmic artery
- May involve aorta

Giant cell arteritis

- Headache
- If pain and stiffness of the hip and shoulder girdles (Polymyalgia rheumatica)
- Jaw claudication
- Scalp tenderness (“It hurts to comb the hair”)
- Fever (16% of fever of unknown origin in older patients)
- Visual changes include amaurosis fugax, blurred vision, eye pain, and blindness.
- Erythrocyte sedimentation rate markedly elevated (100mm/hr).

Giant cell arteritis

- Normochromic, normocytic anemia.
- 20-30% have elevated alkaline phosphatase
- T-cell mediated reaction to vessel wall antigens
- 2/3 have anti-endothelial cell and anti-smooth muscle antibodies
- Temporal artery biopsy shows vasculitis with granulomas.
- Treat with high dose corticosteroids for 6-12 months.
- Sariluimab (IL-6 inhibitor) if steroid failure.
- Treatment begins before biopsy obtained as blindness may develop within 1-2 days of onset.

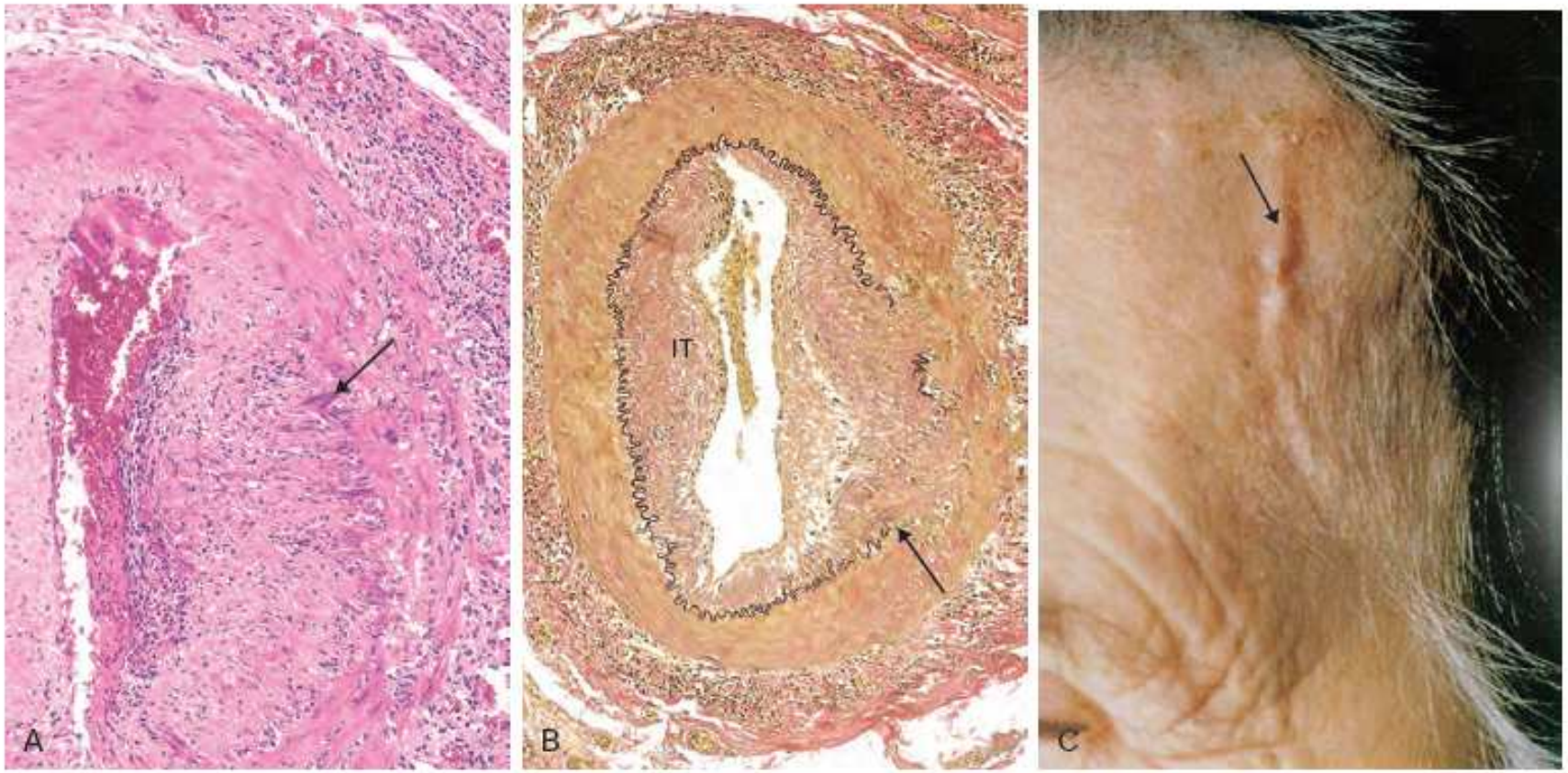
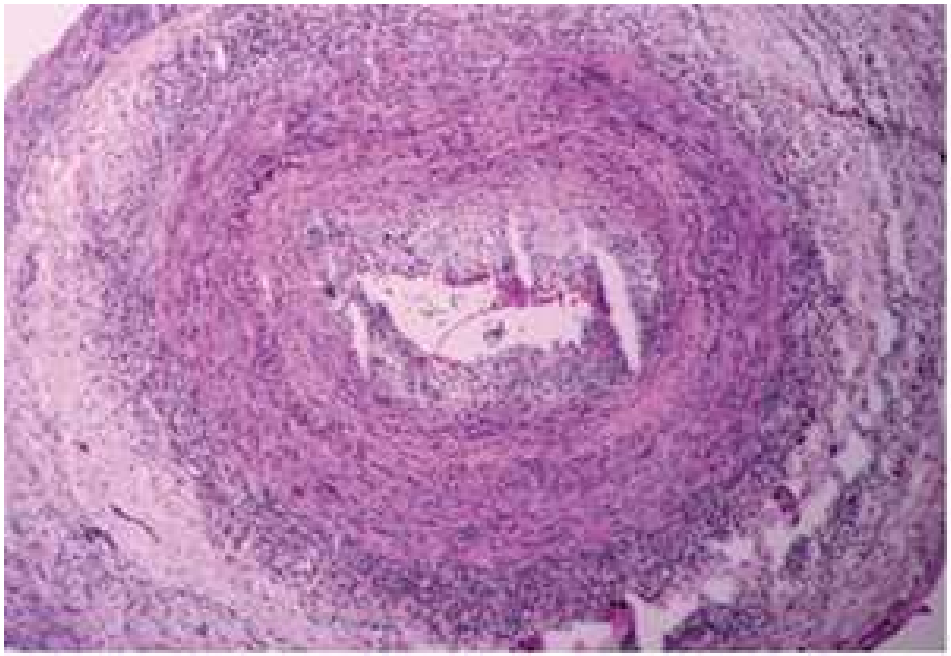


Figure 11-24 Giant cell (temporal) arteritis. **A,** Hematoxylin and eosin stain of section of temporal artery showing giant cells at the degenerated internal elastic lamina in active arteritis *(arrow)*. **B,** Elastic tissue stain demonstrating focal destruction of internal elastic lamina *(arrow)* and intimal thickening (IT) characteristic of long-standing or healed arteritis. **C,** The temporal artery of a patient with classic giant cell arteritis shows a thickened, nodular, and tender segment of a vessel on the surface of head *(arrow)*. (**C,** From Salvarani C, et al. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 347:261, 2002.)

Giant cell arteritis



This temporal artery biopsy demonstrates a panmural infiltration of mononuclear cells and lymphocytes that are particularly seen in the media and adventitia. Scattered giant cells are also present.

Fig. 386e-20 Accessed 02/04/2016

Takayasu's arteritis

- Presents with fever, arthralgias, and weight loss
- <40 years of age.
- Predilection for East Asians, women (9:1)
- Vessel pain and tenderness develop.
- Large vessel disease.
- Involves the aortic arch.
- May involve coronary arteries (15%), pulmonary arteries (15%), renal arteries as well.
- Unequal pulses in the extremities
- Claudication
- Fibrosis of affected vessels leads to "pulseless disease."

Takayasu's arteritis

- Histologically:
- Intimal hyperplasia
- Transmural thickening of aortic wall
- Biopsy shows polyarteritis with granulomas.
- Arterial stenosis and irregularity noted on arteriography.
- Corticosteroids and cyclophosphamide for treatment.

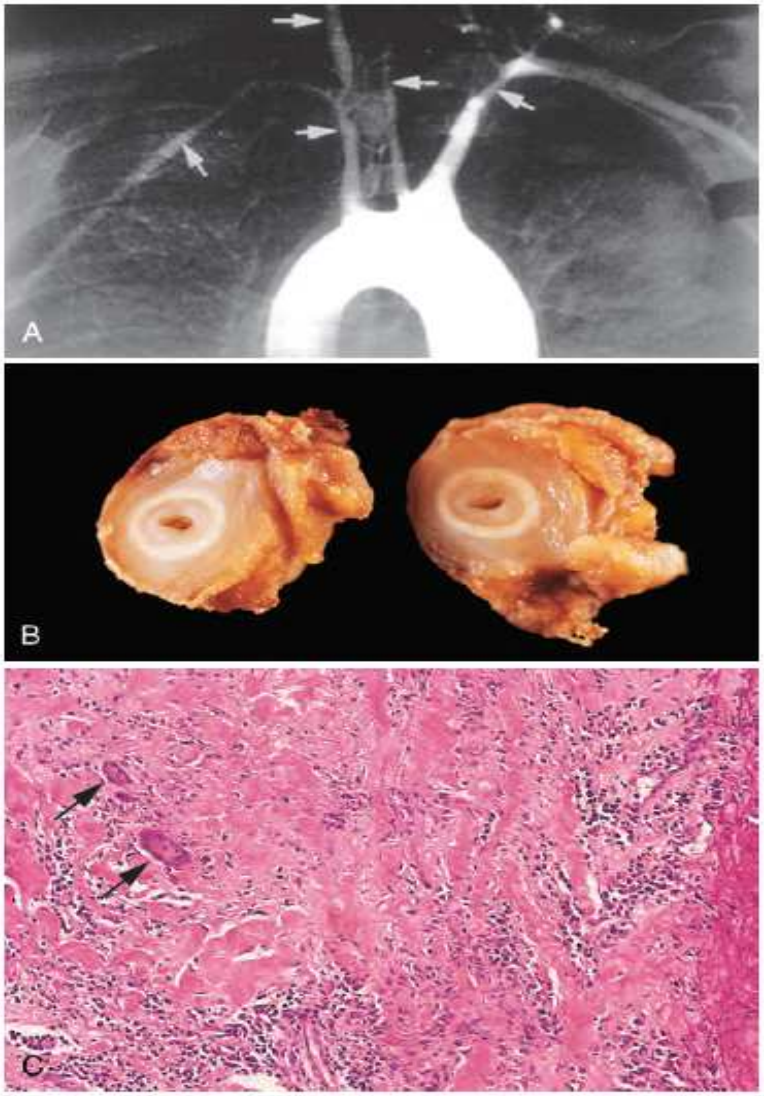
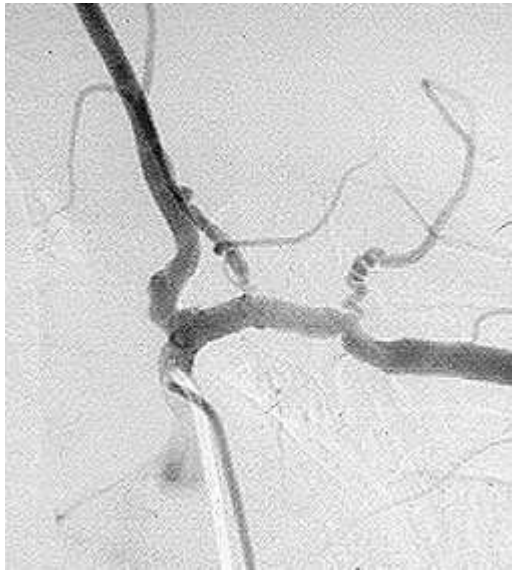
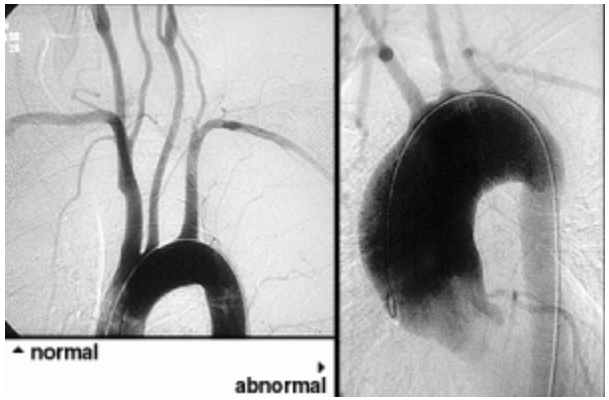


Figure 11-25 Takayasu arteritis. **A,** Aortic arch angiogram showing narrowing of brachiocephalic, carotid, and subclavian arteries *(arrows)*. **B,** Gross photograph of two cross-sections of the right carotid artery taken at autopsy of the patient shown in **A,** demonstrating marked intimal thickening and adventitial fibrosis with minimal residual lumen. **C,** Histologic appearance in active Takayasu aortitis, illustrating destruction and fibrosis of the arterial media associated with mononuclear infiltrates and inflammatory giant cells *(arrows)*.

Takayasu's arteritis



Above: Note the narrowing and irregularities that occur at several sites, and the "corkscrew" configuration of one vessel segment near the junction of the two arteries. These changes, caused by inflammation in the blood vessel wall, sometimes cause complete blockage of the artery.



Right: Normal aortic arch on the left, with narrow, smooth blood vessels. On the right is an example of an abnormal aortic arch in a patient with Takayasu's, with obvious dilation of the ascending aorta on the left side of the picture.

https://www.hopkinsvasculitis.org/types-vasculitis/takayasus-arteritis
Accessed 02/20/2020

Henoch-Schöenlein purpura

- 90% Children.
- Presents 10 days after upper respiratory infection.
- Purpuric rash on the extensor surfaces and buttocks.
- May see lower extremity arthralgia.
- Colicky abdominal pain.
- May be associated with intussusception.
- Associated with focal progressive glomerulonephritis.

Henoch-Schöenlein purpura

- Elevated serum IgG and IgA.
- Biopsy shows vasculitis with IgA and complement deposition.
- Responds to corticosteroids.
- Rapid clearing with plasmapheresis.

Focal proliferative glomerulonephritis

- IgA nephropathy
- Most common nephropathy world-wide.
- ages 10 - 29 years
- usually males
- May present with gross or microscopic hematuria after respiratory infection but no evidence of systemic disease
- More common in southern Europe, Asia and Native Americans
- Less common in individuals of Sub-Saharan lineage
- Up to 15% have systemic disorder.
- Related to Hoenich–Schoenlein purpura.

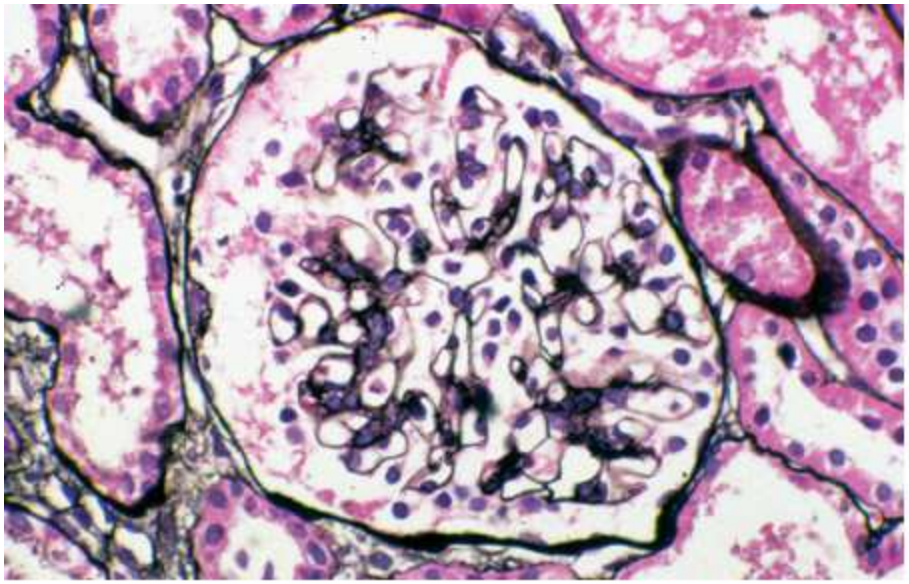
Focal proliferative glomerulonephritis

- Excess amounts of poorly galactosylated serum immunoglobulin IgA1 trigger the generation of glycan specific IgG and IgA autoantibodies,
- Alternate complement pathway activated.
- Focal epithelial cell proliferation.
- No inflammation.
- Polyclonal IgA1 deposition in mesangium.
- IgG, IgM, and/or C3 may be deposited as well.
- Dense deposits in mesangial cells and in paramesangium on electron microscopy.

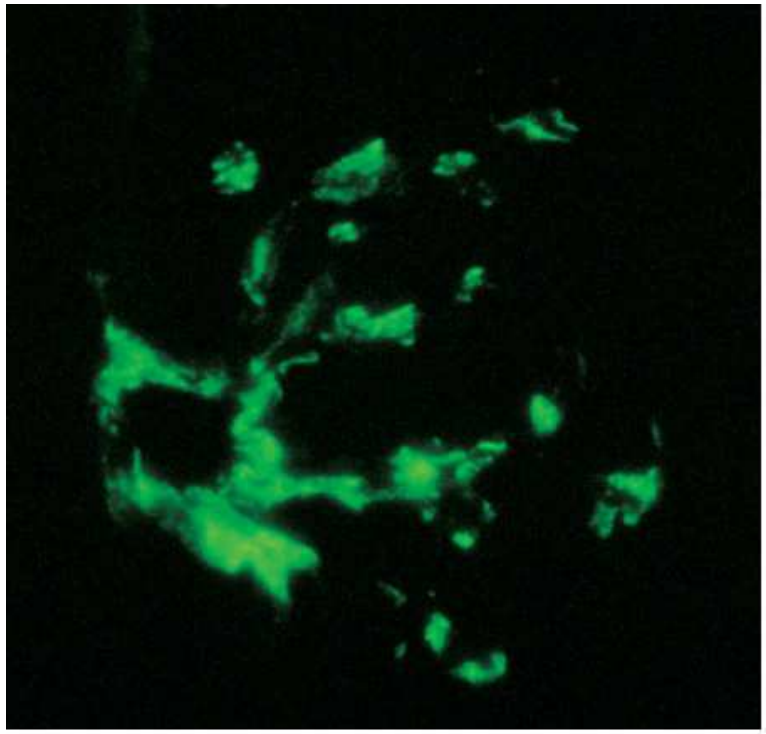
Focal proliferative glomerulonephritis

- Slowly progressive
- 25 - 50% have renal failure at 20 years
- 20% recur after transplantation
- Secondary disease:
- May also see in microangiopathic hemolytic anemia and thrombocytopenia (hemolytic uremic syndrome).
- May be seen in celiac disease or in liver disease where there is defective clearance of IgA complexes.

IgA nephropathy



(ABF/Vanderbilt Collection.) Fig. E9-6 Accessed 03/01/2010



There is variable mesangial expansion due to mesangial deposits, with some cases also showing endocapillary proliferation or segmental sclerosis (left). By immunofluorescence, deposits are evident (right).

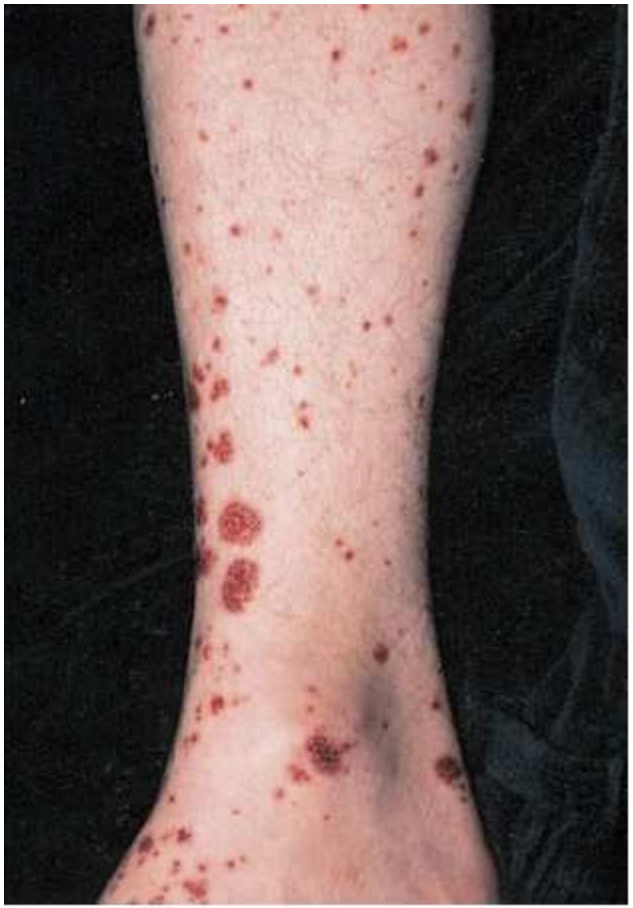
Microscopic polyangitis

- Leukocytoclastic angiitis.
- Type III hypersensitivity.
- Abrupt onset of palpable purpura (erythematous lesions do not blanch on pressure).
- Most common on lower limbs and in dependent areas.
- Cutaneous ulceration and transient arthralgias.
- Vasculitis (and venulitis) with eosinophilia and neutrophilia.
- Fragmented leukocytes present.

Microscopic polyangitis

- 90% will have necrotizing changes in glomeruli; present with hematuria
- Hemoptysis or gastrointestinal bleeding if those organs involved
- C5a anaphylatoxin.
- MPO-ANCA present.
- Erythrocyte sedimentation rate elevated.

Microscopic polyangitis



Palpable purpuric papules on the lower legs are seen in this patient with cutaneous small-vessel (leukocytoclastic) vasculitis.

Lesions of same age.

(Courtesy of Robert Swerlick, MD; with permission.)

Fig. e10-70 Accessed 07/16/2010

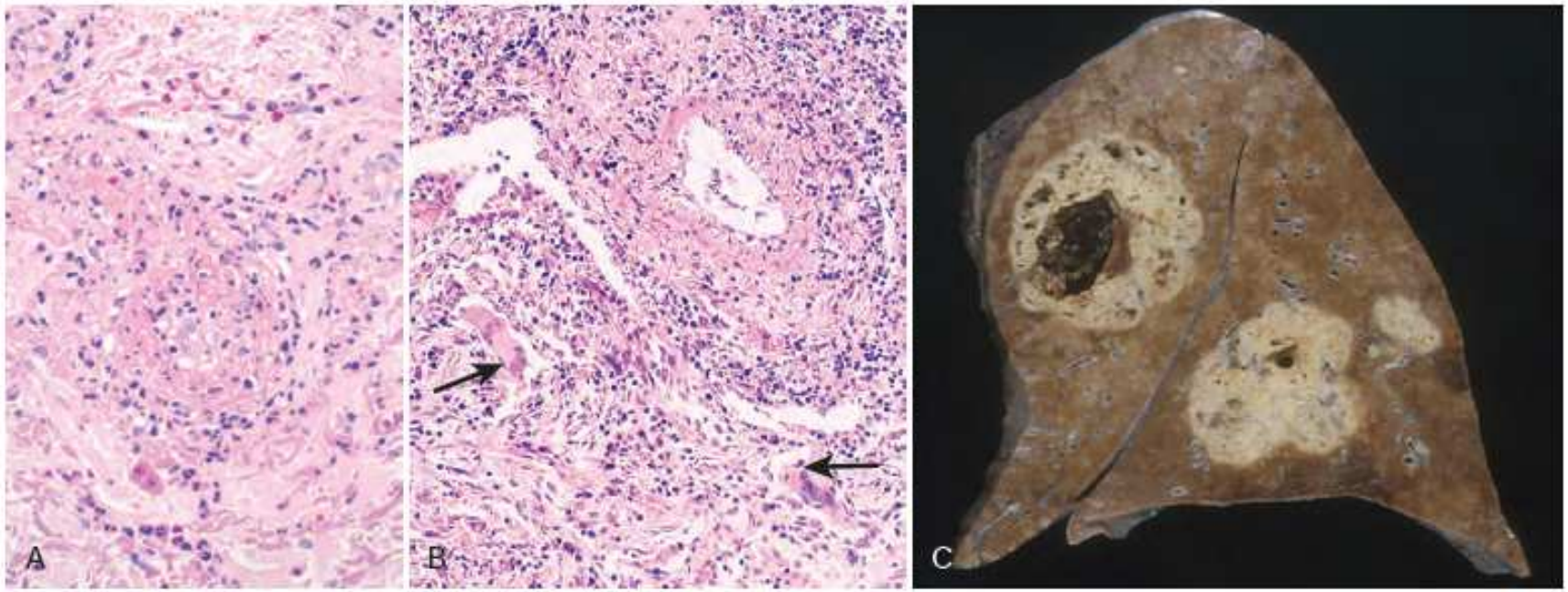
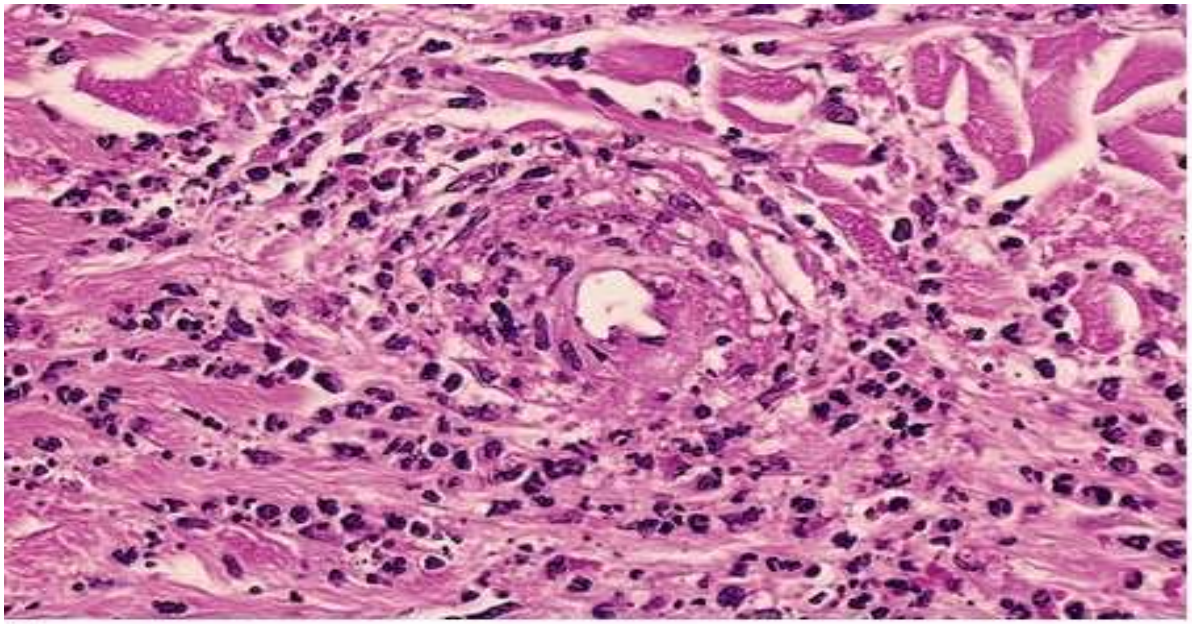


Figure 11-27 Small vessel vasculitis. **A,** Leukocytoclastic vasculitis (microscopic polyangiitis) with fragmentation of neutrophils in and around blood vessel walls. **B** and **C,** Granulomatosis with polyangiitis. **B,** Vasculitis of a small artery with adjacent granulomatous inflammation including epithelioid cells and giant cells *(arrows)*. **C,** Gross photo from the lung of a patient with fatal granulomatosis with polyangiitis, demonstrating large nodular centrally cavitating lesions. (**A,** Courtesy Scott Granter, MD, Brigham and Women's Hospital, Boston, Mass.; **C,** Courtesy Sidney Murphree, MD, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Microscopic polyangitis



A

Perivenular infiltrate of neutrophils with fibrin deposition. (Hematoxylin and eosin stain, x50 in original magnification.)

Fig. 164-6 Accessed 07/20/2010

Burger's disease

- Once known as thromboangitis obliterans
- 20-40 year old men
- Heavy smokers
- Antibody to some element in tobacco hypothesized
- A similar lesion has been described in marijuana users
- Common in Orient, Middle East, South Asia
- Rare in blacks

Burger's disease

- Presents with claudication or Raynaud's phenomenon
- Necrosis and gangrene of distal digits
- "Corkscrew" appearance of vessels on angiogram
- Histology:
- Acute and chronic inflammation, accompanied by luminal thrombosis.
- The thrombus can contain small microabscesses composed of neutrophils surrounded by granulomatous inflammation.
- May recanalize lumen
- My extend into veins and nerves
- STOP SMOKING

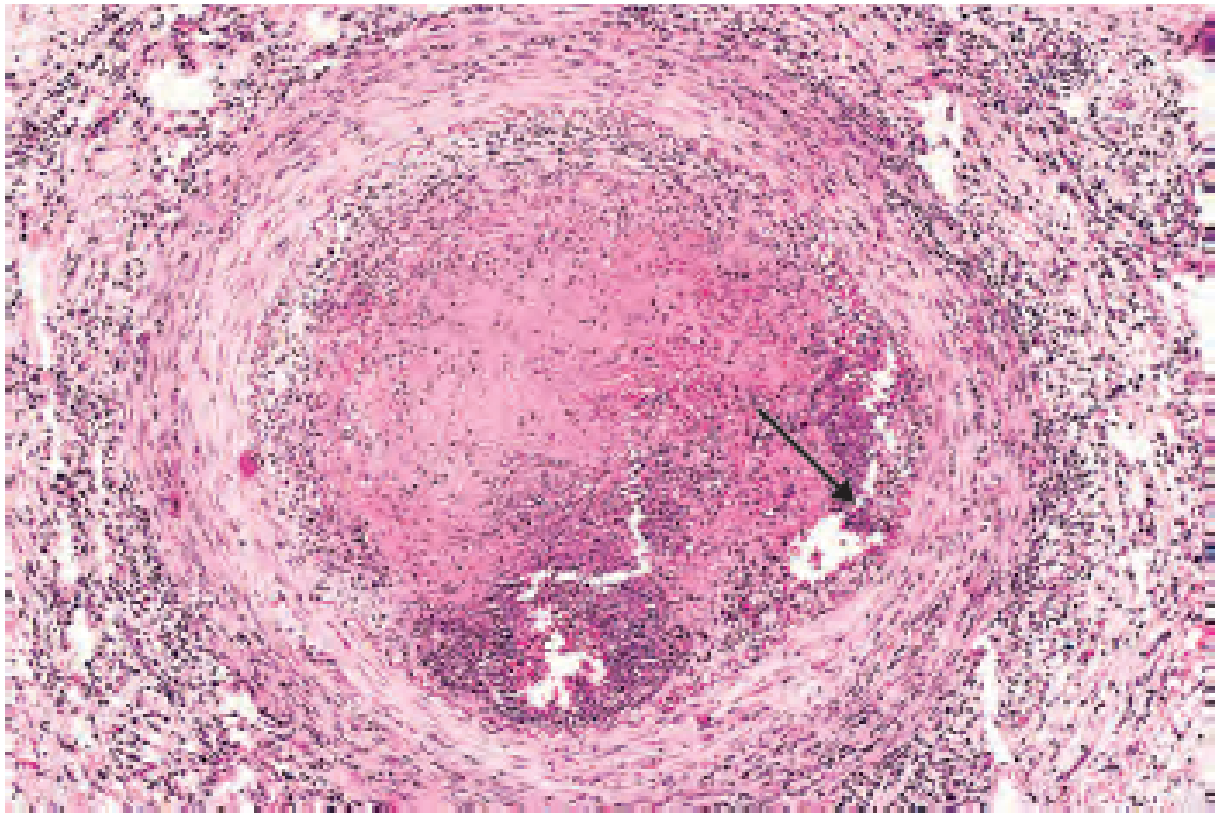


Figure 11-28 Thromboangiitis obliterans (Buerger disease). The lumen is occluded by a thrombus containing abscesses *(arrow)*, and the vessel wall is infiltrated with leukocytes.

Hypersensitivity vasculitis

- Symptoms may be a response to drug exposure (penicillin, aspirin, amphetamines, thiazides, immunization)

  OR infections (streptococcal throat, infection, endocarditis, tuberculosis, hepatitis, staphylococcal)

  OR tumor antigens.
- If drug induced, responds to drug withdrawal and corticosteroid therapy. Treat underlying illness.

Cryoglobulin related vasculitis

- Cryoglobulins have high affinity binding at 4C
- When circulate to warmer tissues, may precipitate
- Type I cryoglobulin
- Does not bind to the Fc fragment of IgG
- Does not easily activate complement
- Asymptomatic until protein concentration causes hyperviscosity syndrome.
- Associated with lymphoma, Waldenström's macroglobulinemia, and multiple myeloma.

Cryoglobulin related vasculitis

- Both types II and III cryoglobulins bind to the Fc fragment of IgG.
- Both types are called mixed cryoglobulins.
- In type II, the immunoglobulin is monoclonal
- Associated with lymphoproliferative diseases
- In type III, the immunoglobulin is polyclonal
- Both types can occur in patients with rheumatic diseases and chronic infections.

Cryoglobulin related vasculitis

- Type II and III cryoglobulinemia frequently present as vasculitis
- Recurrent lower extremity purpura,
- Glomerulonephritis
- Mononeuritis multiplex
- Hepatitis C is the principal cause of mixed cryoglobulinemia.
- Cryoglobulinemia is said to be essential when there is no identifiable underlying disease.

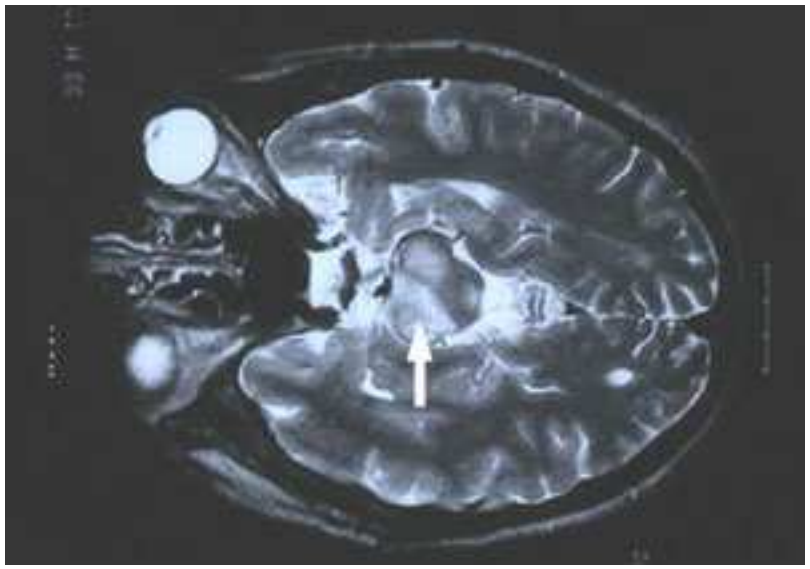
Behçet's disease

- Involves arteries of all sizes and veins as well
- Leading cause of blindness in Japan
- Common in Central Asia
- Anterior uveitis (pain, blurred vision, light sensitivity)
- Posterior uveitis (retinal damage)
- Aphthous ulcers (oral, genital, cecal)
- Erythema nodosum (often ulcerate)
- White matter demyelination
- Aseptic meningitis
- Pulmonary artery aneurysms

Behçet's disease

- HLA-B51 predisposes
- H. pylori implicated
- May see pathergy (prick with sterile needle and pustule will develop within 24 hours)
- Topical steroids, colchicine, and immunosuppressive agents employed

Behçet's disease



MRI demonstrating central nervous system involvement (white matter changes in the pons).

https://www.hopkinsvasculitis.org/types-vasculitis/behcets-disease/ Accessed 02/20/2020

Beçhet's syndrome

- Recurrent oral and genital ulcers, conjunctivitis, arthritis, and focal neurologic deficits.
- Inflammatory.
- Erythrocyte sedimentation rate elevated.
- Non-specific changes on biopsy.
- Type III hypersensitivity.
- HLA-B5 association
- Responds to corticosteroids, colchicine, dapsone, azathioprine, chlorambucil, and cyclosporine.

Mixed connective tissue disease

- Women
- <30 years of age
- Raynaud phenomenon
- Arthritis
- Synovitis of fingers
- Mild myositis
- Pulmonary hypertension
- Trigeminal neuralgia common.

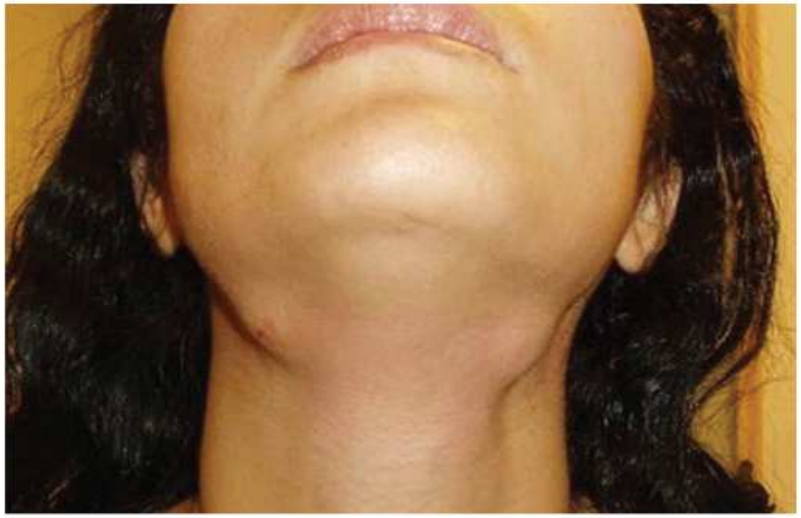
Mixed connective tissue disease

- B-lymphocyte hyperactivity with T-cell activation.
- Vascular endothelial cell proliferation with lymphocyte and plasma cell infiltration of tissue.
- May see secondary Sjögren's syndrome.
- IgG anti-cardiolipin antibodies associated with pulmonary hypertension.
- Anti-RNP antibodies.
- May evolve into SLE or systemic scleroderma

Ig4 related disease

- Autoimmune pancreatitis
- Now identified in other organ systems (salivary glands common)
- Serum IgG4 level exceeding 135 mg/dL
- Histology
- Plasma cell and cytotoxic T cell infiltrate
- >10 IgG4+ plasma cells per high-power field and an IgG4:IgG-positive plasma cell ratio of at least 40%
- Storiform fibrosis
- Obliterative phlebitis
- Responds to anti-CD20 antibody (rituximab)

A



B

A characteristic feature of Ig4 related disease is the propensity to form tumefactive lesions.

A. Lacrimal gland
B. Submandibular gland

Hypersensitivity pneumonitis

- Unlike asthma, which affects the larger airways, hypersensitivity pneumonitis affects the alveolar septae.
- Intense exposure to an antigen, followed by cough and dyspnea within 4-6 hours. Symptoms may last 24 hours following exposure. With repeated exposure, may lead to pulmonary fibrosis.
- May resolve if offending antigen removed.

Hypersensitivity pneumonitis

- Most patients have specific antibodies in their serum (Type III reaction).
- Antibodies to pigeon serum characterizes pigeon breeder's lung.
- Thermophilic actinomycetes found in humidifier characterizes air-conditioner lung.
- Micropolyspora faeni (found in moldy hay) characterizes farmer's lung.
- Proinflammatory cytokines IL-8 and MIP-1α increased in bronchoalveolar lavage fluid. Both CD4+ and CD8+ cells are increased.
- Large numbers of eosinophils suggest eosinophilic pneumonia, microfilarial infection, or aspergillosis.

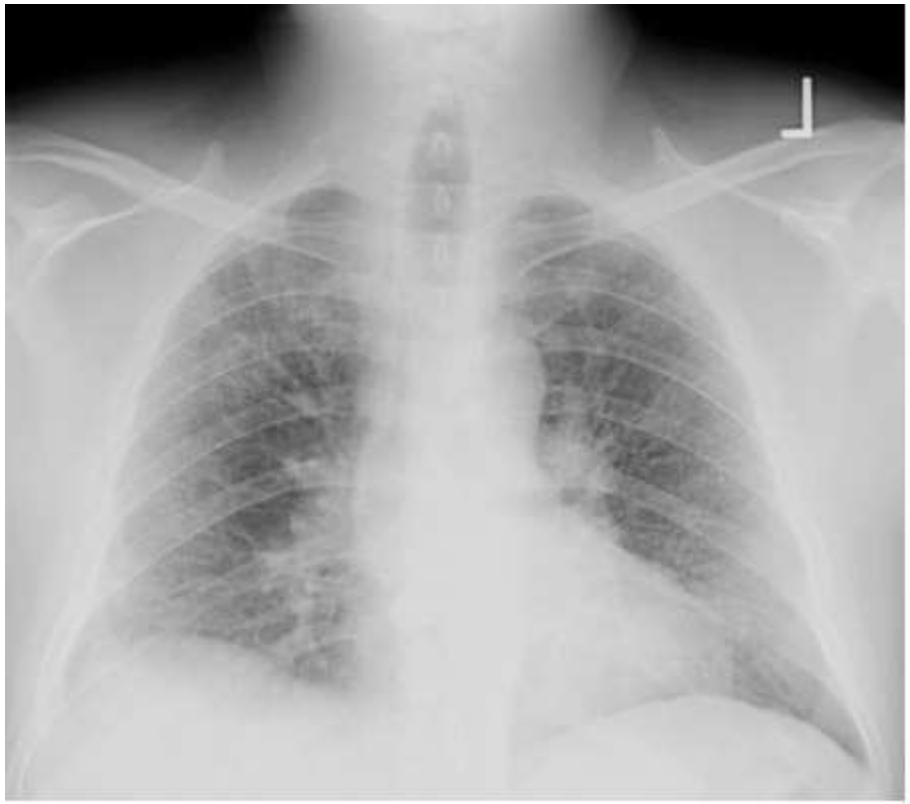
Hypersensitivity pneumonitis

- Centrilobular nodules of ground-glass opacity on x-ray
- A result of repeated episodes of alveolitis
- Exuberant fibroblastic proliferation with alveolar septal fibrosis and alveolar enlargement
- May be patchy and alternate with areas hyperlucency (air trapping in bronchioles).
- Upper lobes.
- The inflammatory response in chronic injury is thought to be of the T_{H2} type.
- Eosinophils, mast cells, and IL-4 and IL-13 are found in the lesions.
- TGF-β expressed at these sites.

Usual interstitial pneumonia/ Idiopathic pulmonary fibrosis

- TGF-β_1 Thought to be driver of the process, however.
- TGF-β_1 negatively regulates telomerase activity, facilitating epithelial cell apoptosis.
- Down-regulates production of caveolin-1, the primary structural protein permitting invaginations in plasma cell membranes
- Associated with receptor mediated endocytosis and with integrin signaling.

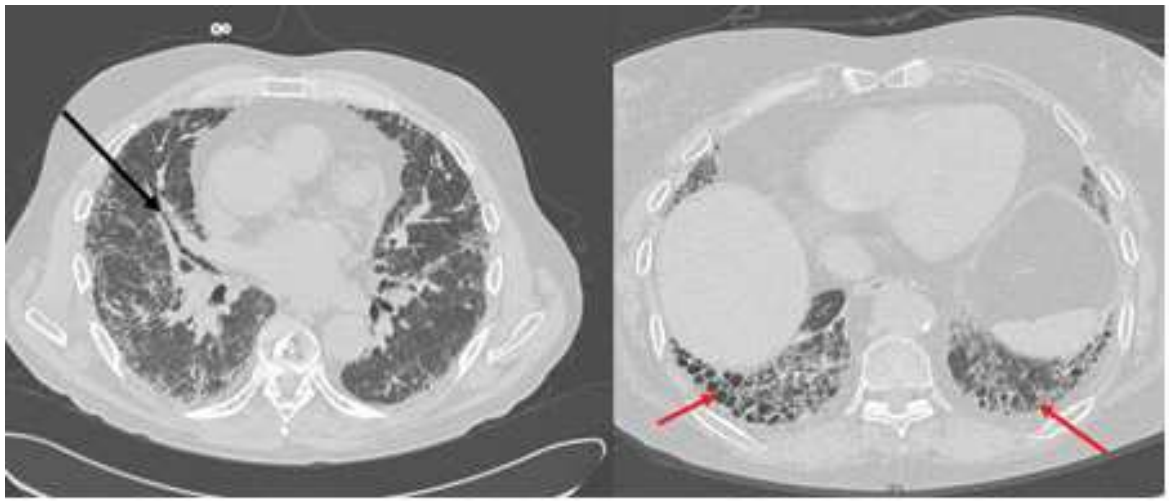
Interstitial disease



Reticular nodular opacities bilaterally with small lung volumes consistent with usual interstitial pneumonitis (UIP). May be referred to as idiopathic pulmonary fibrosis (IPF). In rheumatoid arthritis, was known as Hamman-Rich syndrome.

Fig e24-16 Accessed 03/17/2010

Interstitial disease



Usual interstitial pneumonitis (UIP), also known as idiopathic pulmonary fibrosis (IPF). Classic findings include traction predominance of the honeycombing.

Fig. e24-17 Accessed 03/17/2010

T-cell mediated

- Type IV
- Toxic epidermal necrolysis.
- Staphylococcus antigens; drug induced.
- Multiple sclerosis.
- Myelin basic protein, protolipid protein is the autoantigen.
- Myelin reactive T-cells are found in plaques of multiple sclerosis. (CD4 T_{H1}, T_{H17}, and CD8)

T-cell mediated

- Rheumatoid arthritis.
- Citrulline as antigen.
- Polymyositis, dermatomyositis.
- Psoriasis
- Insulin dependent diabetes mellitus
- Antibody to pancreatic β-cells Inadequate control of effector cells by regulatory T cells.
- Id reaction.

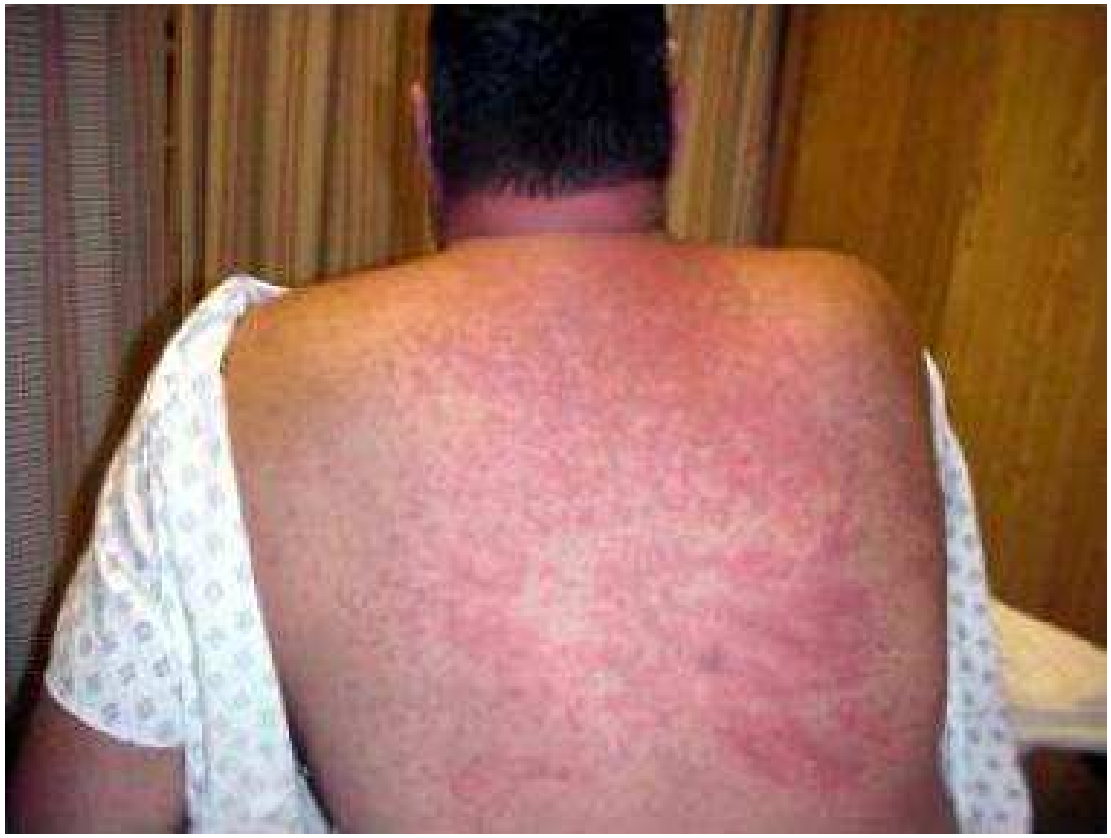
Toxic epidermal necrolysis

- Prodroma of conjunctivitis, pharyngitis, pruritis
- Mucous membrane erosions precede erythema multiforme skin lesions by several days.
- Ocular and genital involvement
- Desquamation
- Drug reaction
- Allopurinol
- Carbamazepine and phenytoin
- Sulfur-containing drugs
- Aminopenicillins
- Oxicam NSAIDs
- Niverapine (NNRTI)

Toxic epidermal necrolysis

- CD8+ cells in blister fluid
- Granulysin (cytokine) level elevated
- Pathogenesis:
- FAS ligand pathway activation
- Granule mediated exocytosis
- Histopathology:
- Apoptotic keratinocyte cell death in the epidermis with dermal-epidermal separation that results in bullae formation.
- Full-thickness lesion
- No antibody demonstrated on direct immunoflourescent stain

Toxic epidermal necrolysis



https://emedicine.medscape.com/article/229698-overview
Accessed 12/07/2019

Toxic epidermal necrolysis

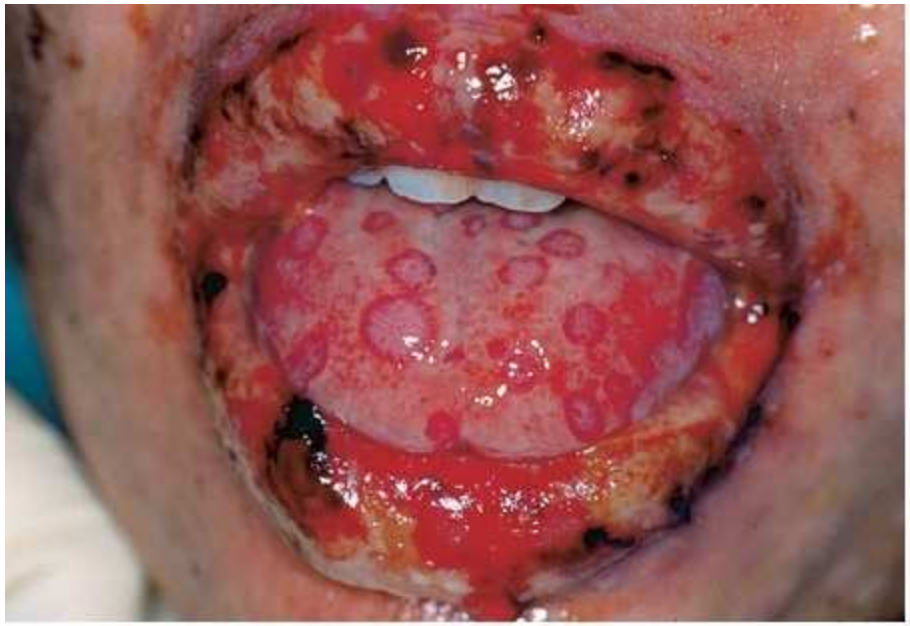


Fig. e7-4 Accessed 07/16/2010

Stevens-Johnson syndrome is part of the TEN spectrum.

Flaccid bullae and vesicles that develop centrally within a pre-existing target lesion.

Widespread apoptosis of keratinocytes provoked by the activation of a cell-mediated cytotoxic reaction.

Rheumatoid arthritis

- Chronic symmetric debilitating and destructive polyarthritis
- Proliferative synovial tissue (pannus) in selected joints
- Men 3:1
- Peak incidence 50-75 years old
- Insidious onset
- Morning stiffness
- May be mono articular in early disease

Rheumatoid arthritis

- 20-30% rheumatoid nodules on extensor surfaces, bursae
- Pain and swelling of pip joints, mcp joints, wrists, knees, ankle, mtp joints, and cervical spine
- 60% small joints only
- 30% large joints only
- C1-2 instability (paresthesias when in flexion)
- Carditis in 50% of patients
- Serositis, pleuritic, mesangial glomerulonephritis, small and medium vessel vasculitis may present as well

Rheumatoid arthritis

- Long standing disease associated with neutropenia and splenomegaly (Felty's syndrome)
- Secondary Sjögren's
- Pulmonary hypertension may precede joint manifestations in 20%
- NSAIDs and methotrexate to control disease

Rheumatoid arthritis

- 30% of genetic risk associated with HLA-DR4
- 15% concordance in monozygotic twins
- Instigator event is unknown.
- Cartilage antigen, Type II collagen, and glycoprotein 39 are antigens commonly found to react with rheumatoid factor
- Rheumatoid factor is an IgM globulin that binds to Fc of IgG.
- These antibodies may self-associate to form immune complexes.

Rheumatoid arthritis

- High-affinity self-reactive T cells are found.
- There is a large expansion of T cell clones with large numbers of HLA-DR4 surface receptors, principally HLA-DRB1
- Co-modulating conformation of antigen presented to T cells
- Augment B cell antibody production.
- CD4+ and memory T-cells are found in affected joints.

Rheumatoid arthritis

- PTPN22 also involved in rheumatoid arthritis
- encodes a protein tyrosine phosphatase that participates in activation of inflammatory cells.
- IL-1 production is marked.
- TNF-α production is induced .
- Both IL-1 and TNF-α are capable of inducing the production of each other.

Rheumatoid arthritis

- Angiogenesis accompanies the acute inflammatory response.
- TNF-α is secreted.
- Activated T cells expres RANKL
- Activate osteoclasts and may contribute to cartilage loss.
- Immunosenescent lesions contain CD4+ cells that are CD28-
- These are essentially NK cells that do not respond to co-stimulation.

Rheumatoid arthritis

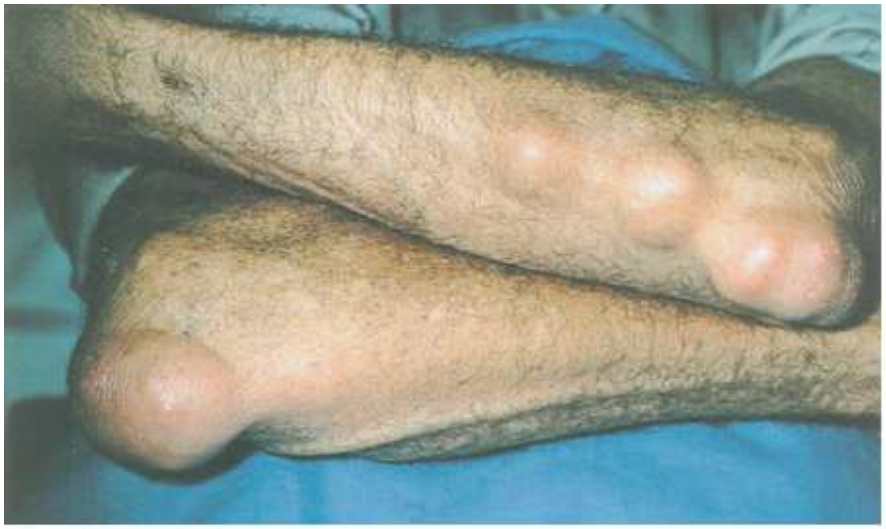
- T_{H17} secreted IL17 and T_{H1}secreted IFN-γ stimulate production of pro-inflammatory materials in synovial cells and macrophages.
- Endothelial cells are then activated, facilitating leukocyte binding.
- Matrix metalloproteinase production increases.

Rheumatoid arthritis

- Citrulline is post translational modification of arginine residues within proteins and peptides
- Necessary for skin formation
- Anti-cyclic citrulline protein antibodies are pathognomonic. Positive likelihood ratio (LR+) of 12.5 with an LR-, 0.3.
- May precede clinical disease by 10-15 years
- Mutated PAD4 may increase citrullination
- Porphyromonas gingivalis contains PAD enzyme
- Associated with aggressive periodontal disease

Rheumatoid nodule

- Major extra-articular manifestation of rheumatoid arthritis.
- Lesions are found in areas of skin subject to pressure.
- They are firm, non-tender subcutaneous nodules.
- Positive likelihood ratio (LR+) >30.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Fig. e10-75 Accessed 07/01/2010

Rheumatoid nodule

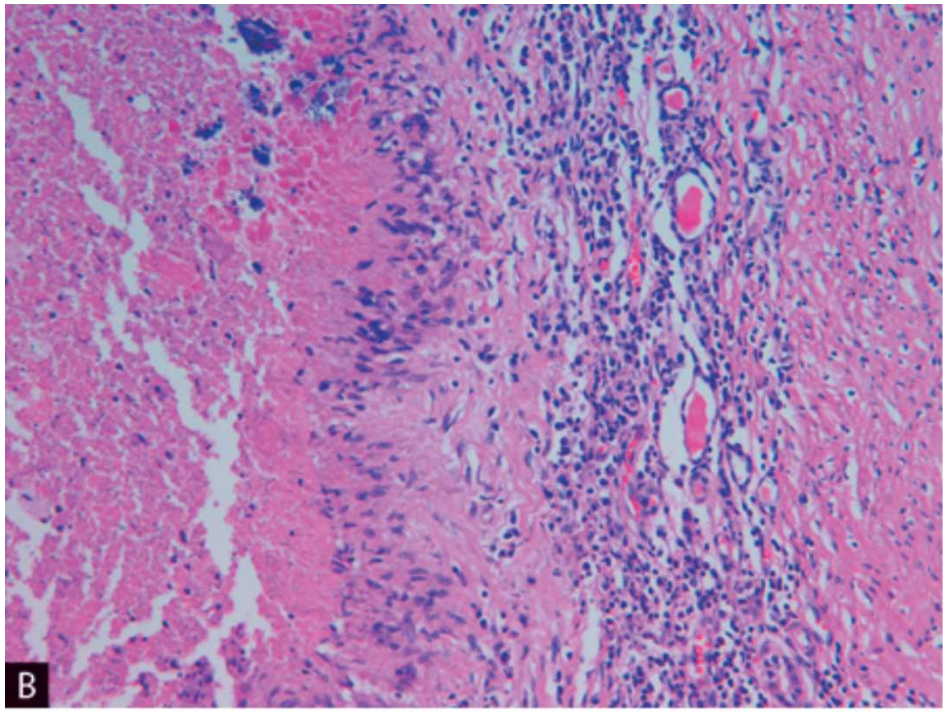


Figure 3-3B Accessed 02/03/2016

Subcutaneous rheumatoid nodule with an area of necrosis (top) surrounded by a palisade of macrophages and scattered chronic inflammatory cells.
H&E 400x

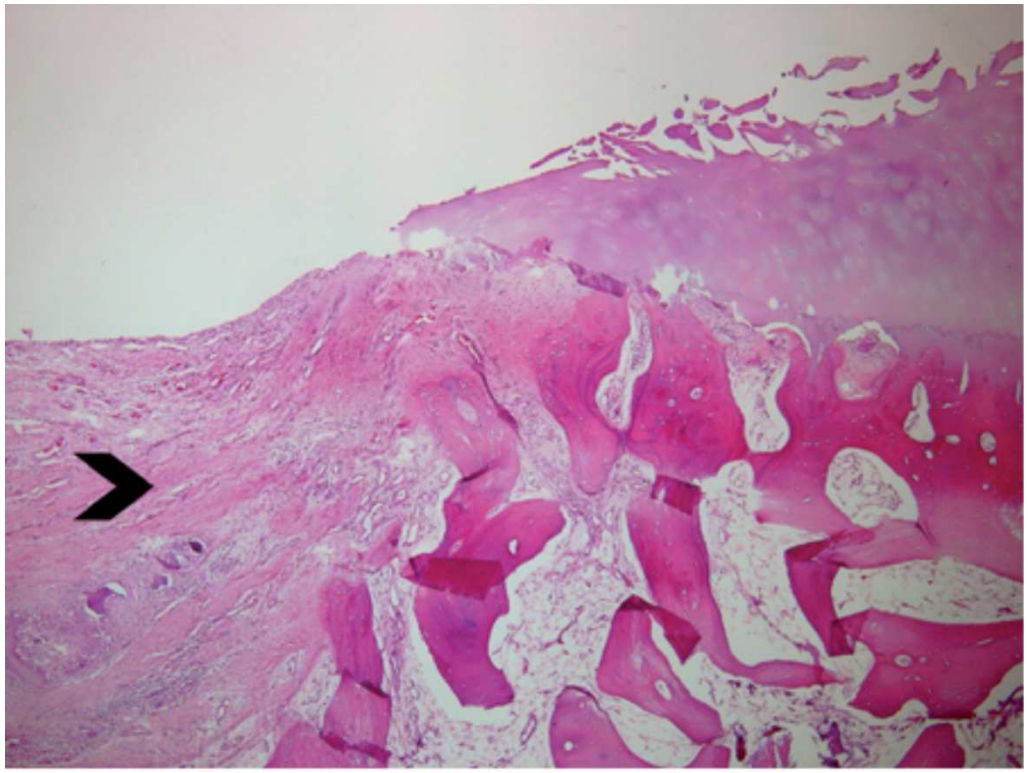
Rheumatoid granuloma

- Microscopically there is a central zone of fibrinoid necrosis rimmed by epithelioid histiocytes and lymphocytes (B, CD4 Th1, and CD28- T cells).
- Pannus is characterized by synovial cell proliferation associated with focal collections of lymphocytes and a reactive fibrosis.

Rheumatoid arthritis

- Synovium of joints involved
- Synovial membrane anchored to underlying capsule and does not cover the articular surface of the joint
- The synovial membrane is lined by
- Type A synoviocytes (specialized macrophages)
- Type B synoviocytes synthesize hyaluronic acid
- Similar to fibroblasts
- Synovial membrane lacks a basement membrane
- Permits efficient exchange between blood and, synovial fluid
- Synovial fluid is a hyaluronic acid containing plasma filtrate

Pannus



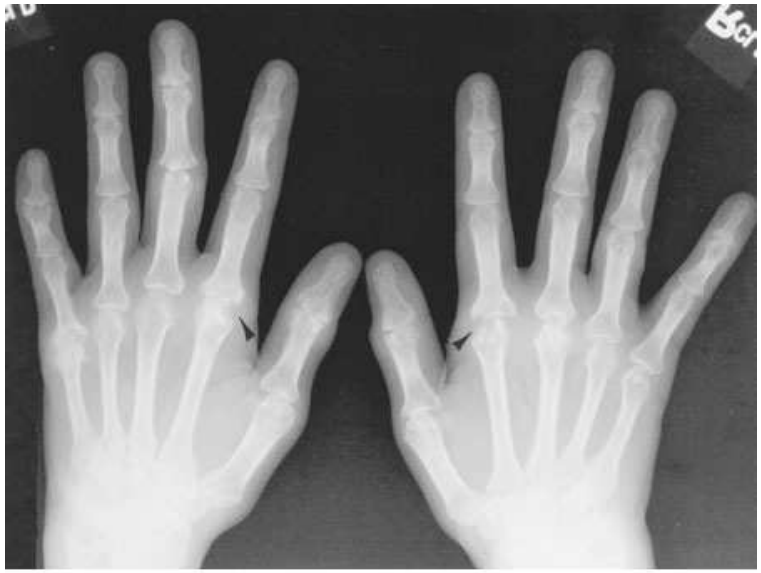
Source: Kemp WL, Burns DK, Brown TG: *Pathology: The Big Picture*: www.accessmedicine.com

Figure 19-10 **Accessed 02/03/2016**

The inflammation associated with rheumatoid arthritis can lead to fibrosis of synovial tissues (arrowhead) and fusion of the joint (ankylosis).

Hematoxylin and eosin, 40×.

Rheumatoid arthritis



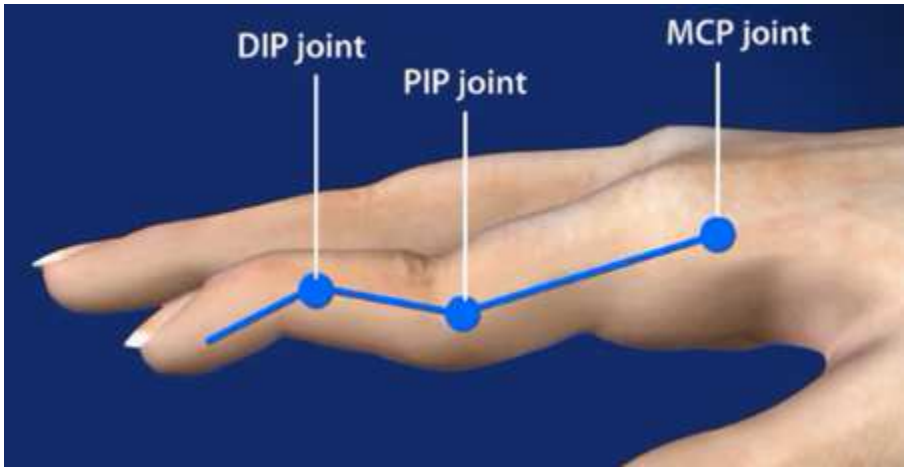
Frontal view of both hands in a patient with long-standing rheumatoid arthritis showing marked carpal destruction and radiocarpal joint narrowing with substantial erosive change as well as the characteristic "bare area" erosions best exhibited at the second metacarpo-phalangeal joint (*arrowheads*).

Also note the soft-tissue swelling at multiple joints.

Deviation of digits is a late change.

Fig. 7-42 Accessed 08/01/2010

Rheumatoid arthritis



"Swan neck" deformity

https://www.handandwristinstitute.com/wp-content/uploads/Symptoms.jpg
Accessed 12/10/2019

Rheumatoid lung disease

- Once referred to as Hamman-Rich syndrome.
- Diffuse alveolar damage resulting from "repeated cycles" of acute lung injury (alveolitis).
- There is damage to alveolar epithelial cells (with secondary microvascular injury) and Type II pneumocyte hyperplasia.
- Reparative changes at these sites give rise to exuberant fibroblastic proliferation and fibrous nodules.
- Both non-caseating granulomata and vasculitis are found in active rheumatoid arthritis involving the lung.

Rheumatoid lung disease

- Mediators of repair such as TGF-β are expressed at these sites.
- The inflammatory response is thought to be of the T_{H2} type.
- Thus, eosinophils, mast cells, and IL-4 and IL-13 are found in the lesions.
- Pulmonary capillary hydrostatic pressure is usually not elevated
- Hemodynamic factors play a secondary role.

Indicators of poor prognosis in rheumatoid arthritis

- Female sex
- Functional disability
- Number of joints involved
- Older age at onset
- High titer of rheumatoid factor
- HLA-D4, particularly if homozygous
- Extra-articular manifestations, particularly if vasculitis or skin nodules
- Structural damage or deformity
- Uncontrolled polyarthritis

Management of rheumatoid arthritis

- NSAIDs remain an important component of pharmacotherapy because of their analgesic and anti-inflammatory properties.
- Early aggressive therapy with disease modifying anti-rheumatic drugs (DMARDs) has become the standard of care.
- Methotrexate is the drug of choice for monotherapy.
- Gold and antimalarial agents inhibit the induction of TNF-α and IL-1
- Methotrexate acts as general immuno-suppressant.

Management of rheumatoid arthritis

- Etanercept reduces circulating TNF.
- Treatment-naïve patents, those with DMARD-refractory RA, and those with moderately to severe active RA
- Not recommended in patients with congestive heart failure or with demyelinating disease
- Fever and chills with intravenous infusion are common (cytokine release).
- Sarucimab (IL-6 inhibitor) in DMARD failure.
- They may be used in combination with methotrexate.

Polymyositis, dermatomyositis, inclusion body myositis

- T-cell mediated cytotoxic process against yet undescribed muscle antigens.
- HTLV-1, HIV, Coxsackie B, Influenza, Hepatitis B as triggers.
- EBV may cause a similar picture but involves additional muscle groups (e.g., tongue)
- Penicillamine, ACE inhibitors, procainamide, statins as medication triggers.
- C5b-9 may be found in capillary vessels
- Respond to corticosteroids, intravenous immunoglobulins, high protein diet.
- 80% 5 year survival

Polymyositis

- Polymyositis is more common in blacks, women.
- Rare in Japanese.
- Rarely affects children.
- Patients usually 45-50 years of age.
- Symmetrical, usually painless
- Proximal muscle weakness.
- Weakness of neck flexors

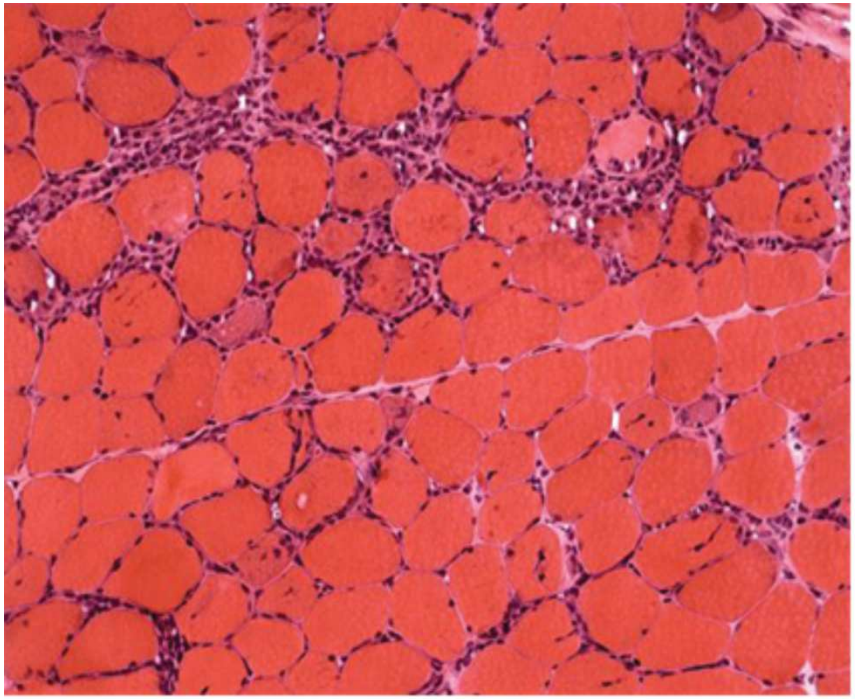
Polymyositis

- Anti-histidyl-tRNA synthetase (Jo-1) is found in 20-30% of patients.
- The presence of anti-Jo-1 antibodies defines a distinct group of polymyositis patients with interstitial lung disease, arthritis, and fevers.
- The anti–Jo-1 response appears to be self-antigen driven, having a broad spectrotype over time and undergoing isotype switching.
- Interstitial lung disease a common complication.

Polymyositis

- Patients with anti-SRP (RNA protein complex) antibodies have acute polymyositis with cardiac involvement, a poor prognosis, and a poor response to therapy.
- Anti-SSa and anti-SSb may also be found.
- Creatine kinase, aldolase enzyme levels elevated.

Polymyositis



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Accessed 02/03/2016

Cross-section of a muscle biopsy from a patient with polymyositis demonstrates scattered inflammatory foci with lymphocytes invading or surrounding muscle fibers (perimysial).

Lack of chronic myopathic features (increased connective tissue, perifascicular atrophy, or hypertrophied fibers) as seen in inclusion body myositis.

H&E, 40X

Dermatomyositis

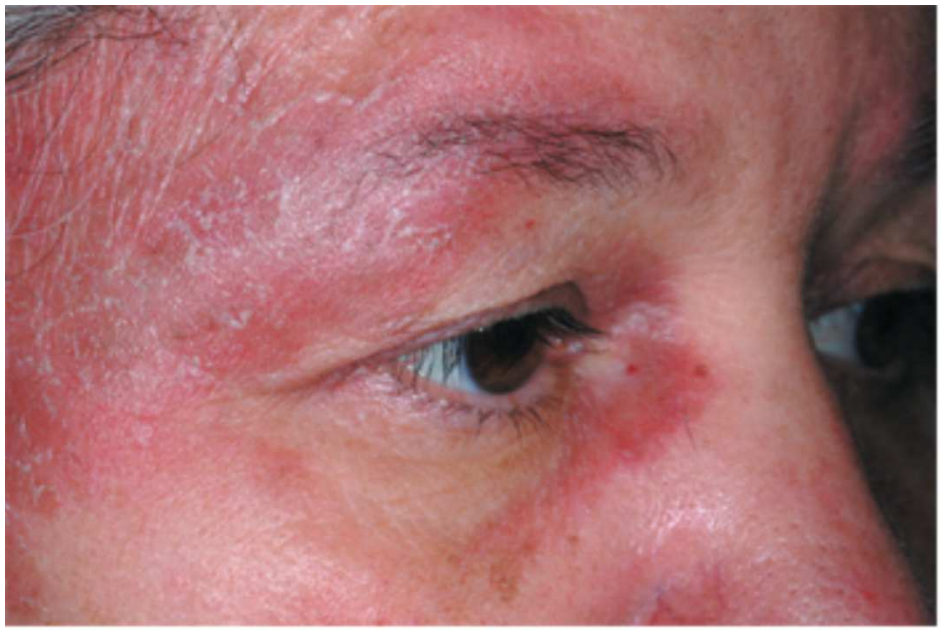
- Dermatomyositis may be seen in children 5-14 years old, but is principally a disease of adults. Symmetrical, usually painless
- Proximal muscle weakness.
- Weakness of neck flexors
- Violaceous rash on head, trunk, hands
- Gottron papules are scaly red eruptions over knuckles, elbows, knees

Dermatomyositis

- Autoantibodies recognizing Mi-2 (nuclear complex protein) are considered specific serologic markers of dermatomyositis.
- They are detected in about 20% of patients with myositis
- Are associated with relatively acute onset, a good prognosis, and a good response to therapy.

- Anti-P155/P140 are found in paraneoplastic and juvenile cases

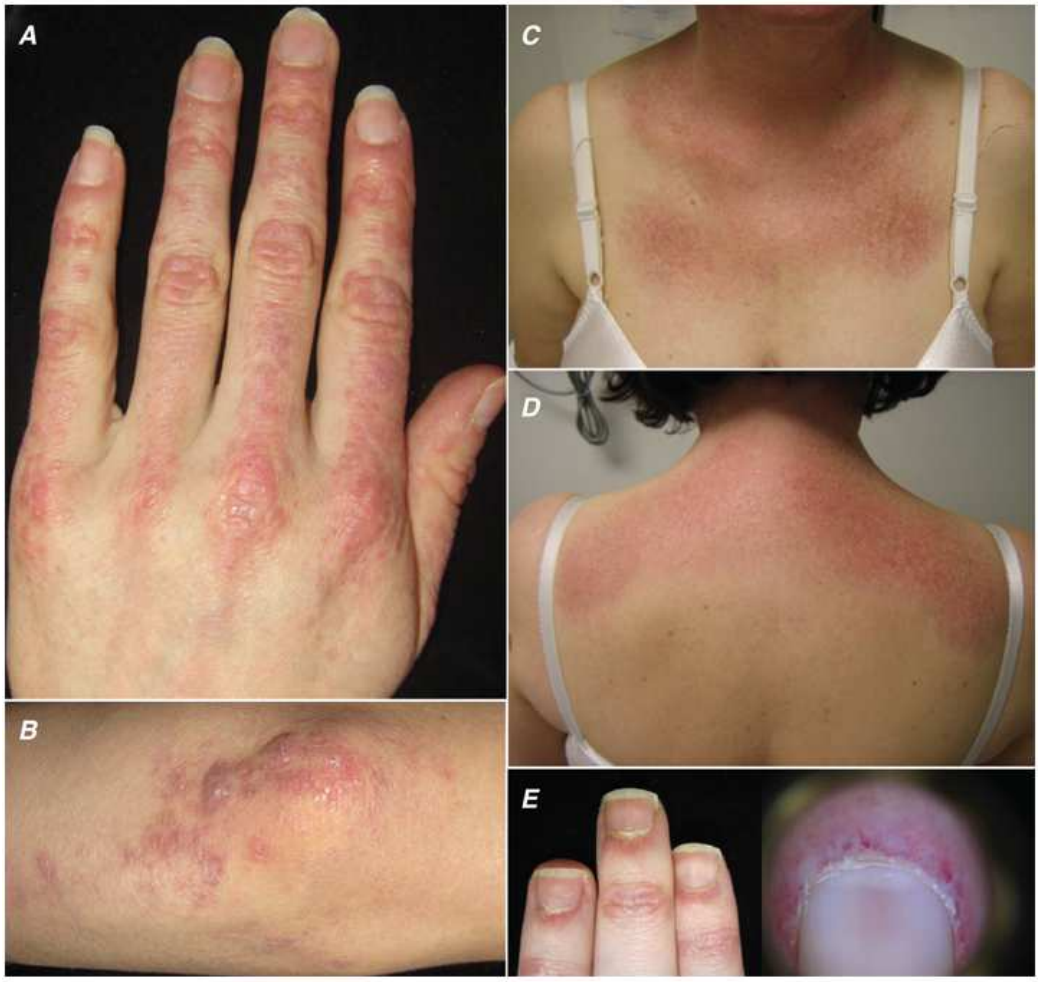
Dermatomyositis



Heliotrope (violaceous) rash around the eyes in a patient with dermatomyositis

(Reproduced with permission from Richard P. Usatine, MD).

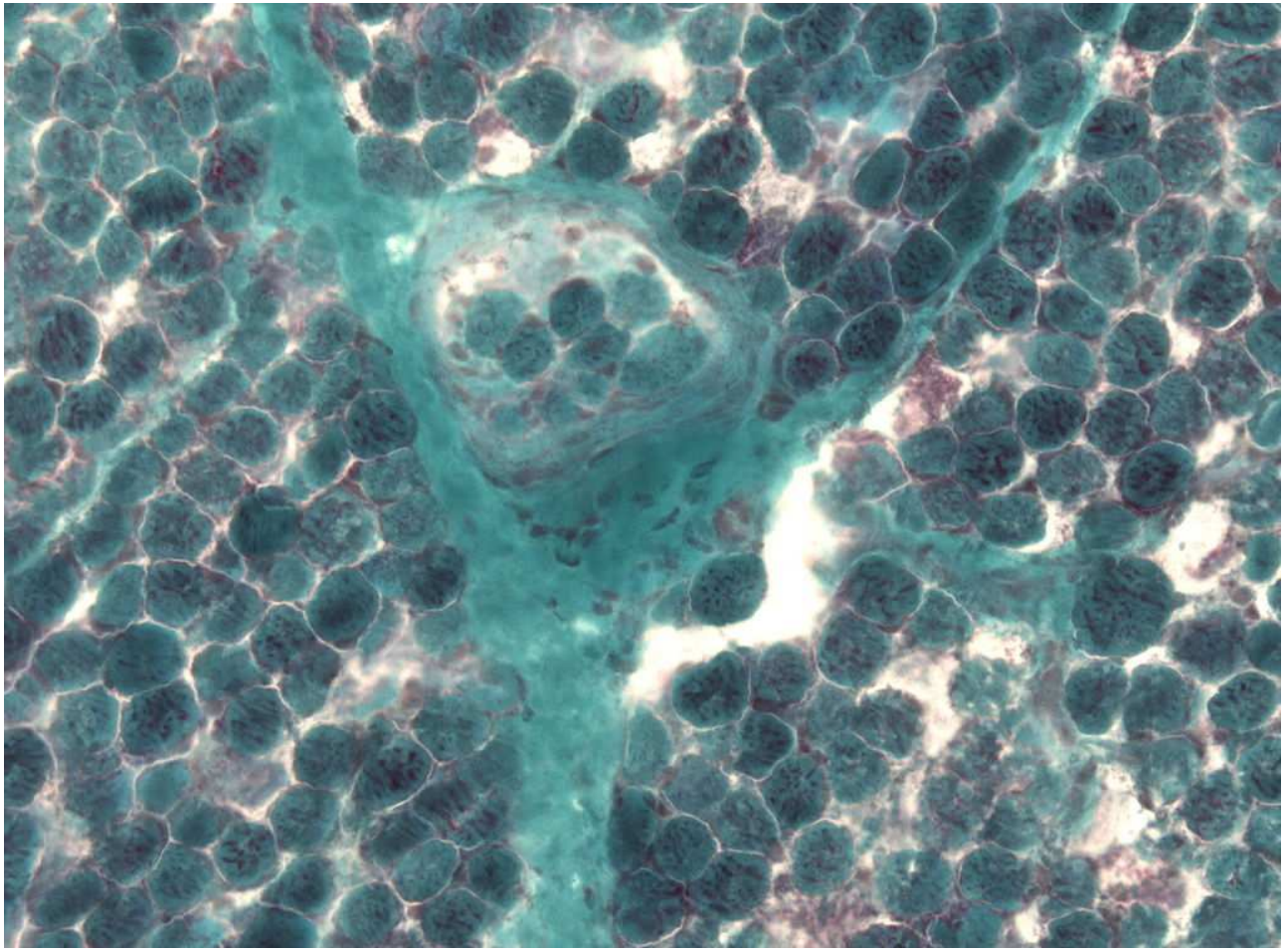
Dermatomyositis



Inclusion body myositis

- Inflammatory myopathy
- Occurs after the age of 50.
- Men
- Quadriceps weakness
- Dysphagia
- Rimmed vacuoles in muscle.
- Ragged red muscle fibers.
- Intracellular deposits of β-amyloid protein, amyloid β-pleated sheet fibrils, and hyperphosphylated tau protein are found.
- HTLV-1 association in 15%

Ragged red fibers



https://en.wikipedia.org/wiki/Leigh_syndrome#/media/File:Leigh_Trichrom.jpg Accessed 03/20/2020

Psoriasis vulgaris

- Characterized by red plaques with silver scales that show petechiae when removed.
- No pustules
- Bilateral but not symmetrical
- Often spares exposed areas
- May be limited to elbows and knees
- May be limited to scalp
- Lumbosacral involvement
- May be limited to penis and anogenital region
- Nail pitting and discoloration in 25% of patients
- Disease may be limited to nails

Psoriasis vulgaris

- If one parent has psoriasis, 8% of offspring develop disease
- If both parents have psoriasis, 41% of offspring develop disease
- 66% HLA-Cw*0602 association
- Indolent disease
- Pruritis common

Psoriasis vulgaris

- Type I
- Early onset disease
- 75%
- Median age for women is 16 years-old
- Median age for men is 22 years-old
- Type II
- Late onset disease
- Median age 56 years-old
- Not seen in Native Americans
- Low incidence in West Africans, Japanese, Eskimos

Psoriasis vulgaris

- Seronegative spondyloarthritis of Reiter's disease type is associated with presence of HLA-B27.
- Seen in 5% of patients.
- Rare before age 20
- Involves sacroiliac joints, hips, cervical spine
- Associated with pustular psoriasis and psoriasis erythroderma
- There is a distal version of seronegative psoriasis that manifests as asymmetrical oligoarthritis
- DIP joints of hands and feet
- No subcutaneous nodules

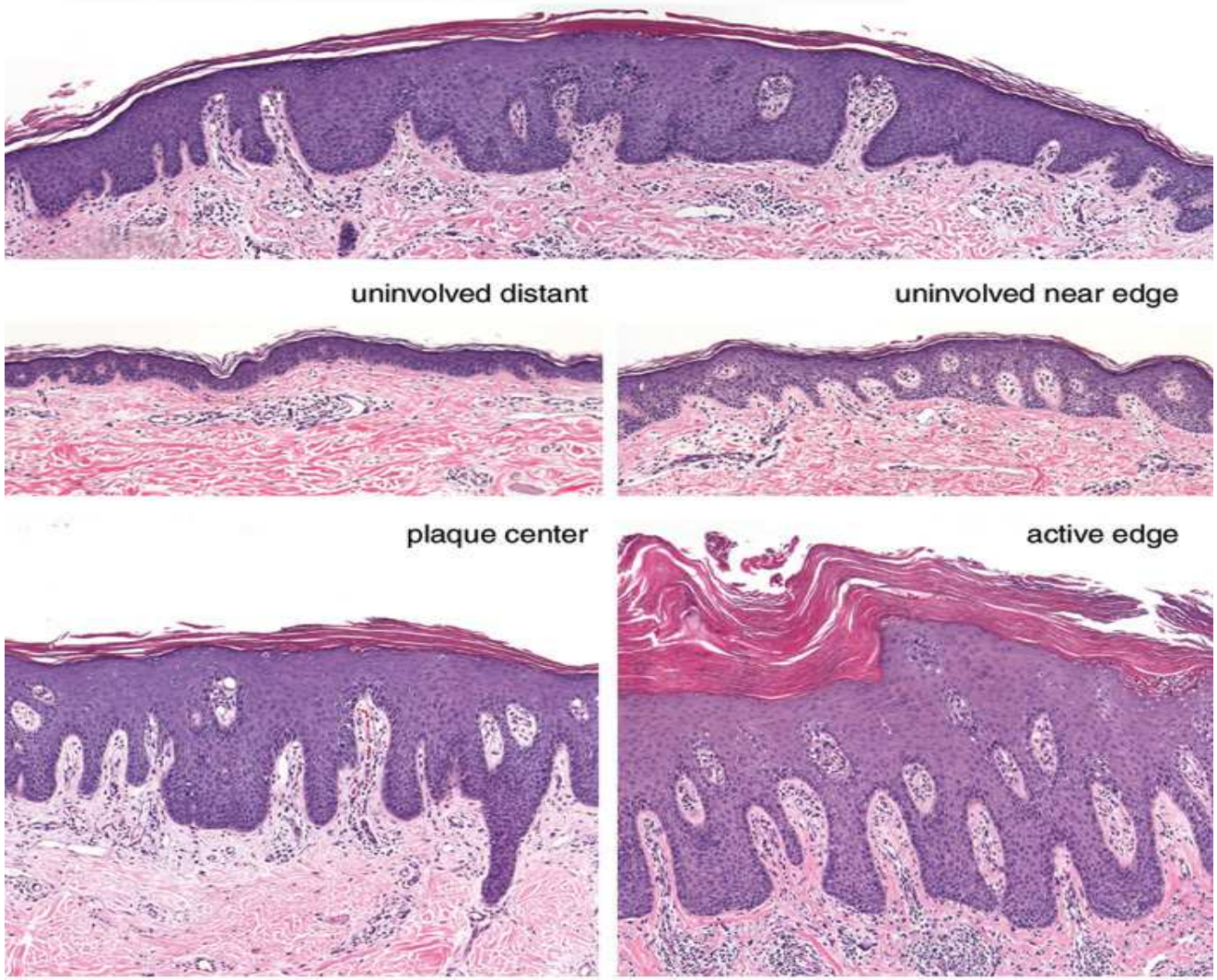
Psoriasis

- Pathogenesis
- T-cell mediated disease.
- CD4+ T_H1 and T_H17 as well as CD8+ cells in epidermis
- TNF is major mediator of the lesion.
- Physical trauma (rubbing and scratching) stimulates the proliferative process
- Stress may lead to disease flares
- Acute onset should prompt check of HIV status

Psoriasis

- Histopathology
- Increased epidermal cell turnover results in epidermal thickening (acanthosis) with downward proliferation of rete ridges.
- Cell cycle shortens from 311 to 36 hours
- Mitoses above basal cell layer.
- Parakeratoses.
- Dermal vessels dilated near papillae. May see small inflammatory infiltrates in epidermis (Munro abscesses).

Psoriasis

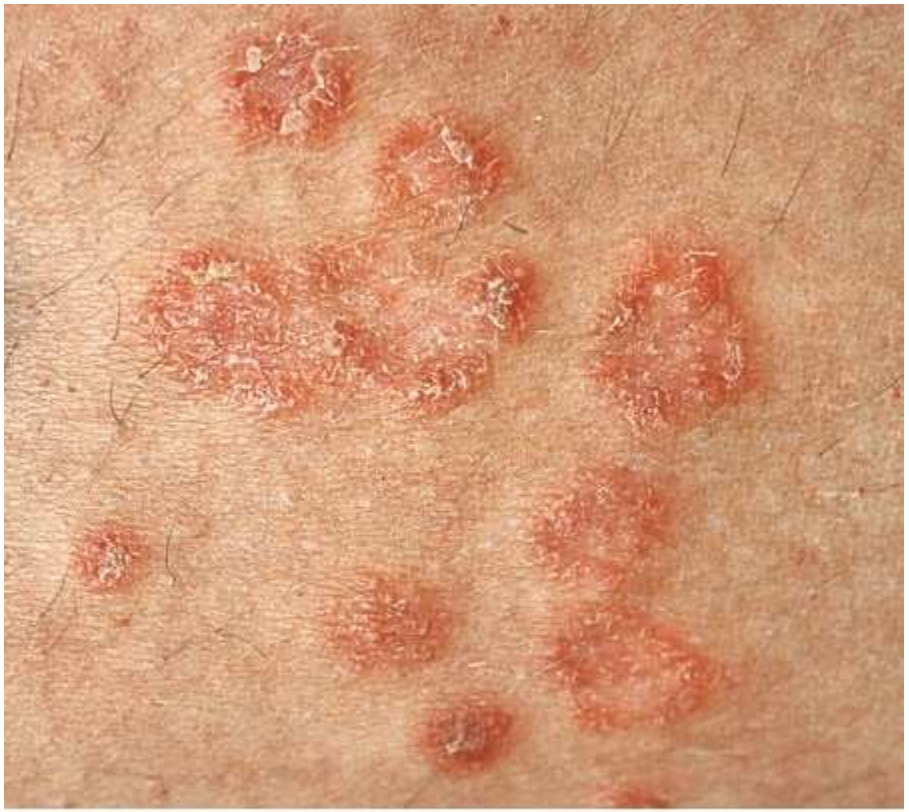


Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ: *Fitzpatrick's Dermatology in General Medicine*, 7th Edition: http://www.accessmedicine.com

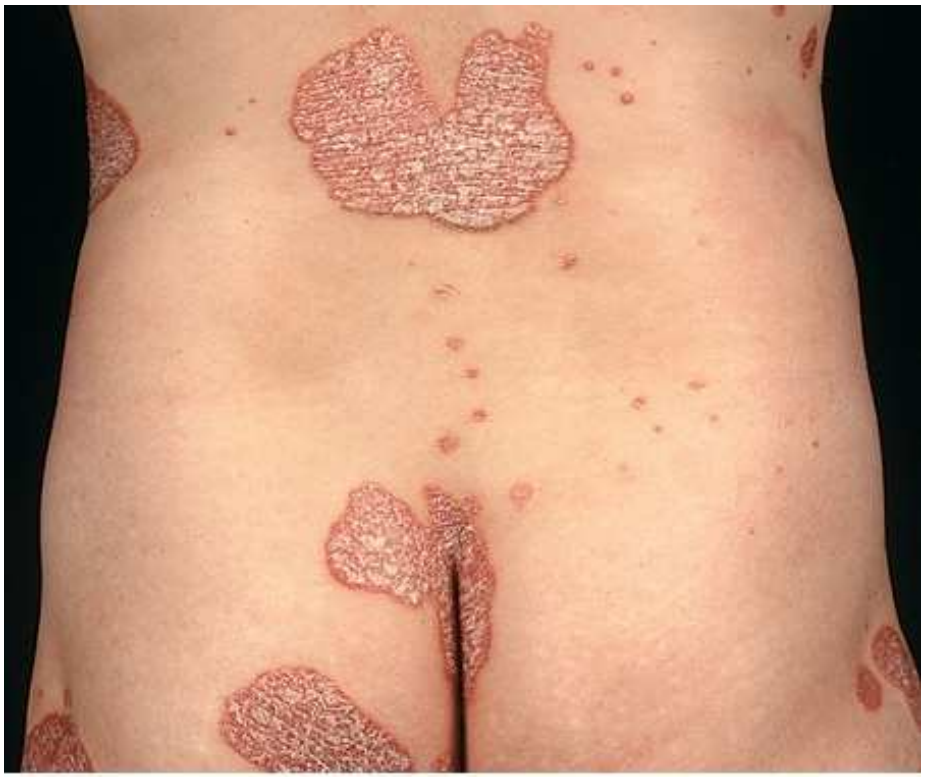
Fig. 18-3 Accessed 04/18/2011

Psoriasis

- Scale Fig. 3-1



Plaque Fig. 3-4 Accessed 07/16/2010



Markers of inflammation

- CRP is a surrogate for IL-6 and is elevated in inflammatory conditions.
- An elevated erythrocyte sedimentation rate may provide similar information
- Minor ANA and RA elevations simply reflect an acute inflammatory response.
- A negative ANA or RA excludes those diseases.

Markers of autoimmune disease

- A markedly elevated titer of ANA with positive dsDNA or anti-Sm is diagnostic of systemic lupus erythematosis.
- An elevated titer of ANA with the presence of anti-histone antibodies is noted in drug induced systemic lupus erythematosis.
- In Sjögren's syndrome, anti-Ssa and anti-SSb are present.
- Anti-Scl70 antibodies are present in diffuse scleroderma.
- Anti-centromere antibodies are present in CREST syndrome.

Markers of autoimmune disease

- Anti-Jo-1 present in dermatomyositis, polymyositis.
- An markedly elevated RA titer (>1:64) is compatible with a diagnosis of rheumatoid arthritis.
- Anti-citrulline antibodies are pathognomonic of rheumatoid arthritis.
- Anti-RNP antibodies in mixed connective tissue disease.

TOLERANCE AND SENSITIZATION

Anergy and tolerance

- As B and T cell specificity is determined by recombination events to create a large repertoire of antigen receptors, those cells reacting with self-antigen must be removed.
- Clonal deletion. B cells undergo receptor editing of the light chain in the bone marrow. If that editing fails to prevent recognition and binding of innate (self) proteins, the B cell is deleted. (Negative selection)
- If the B cell escapes deletion and is weakly binding, is non-functional unless presented with high antigen concentration.

Anergy and tolerance

- If the B cell escapes deletion and is strongly binding and recognizes the antigen in the absence of co-stimulatory molecules, they are stimulated to become permanently anergic. Decreased levels of IgM and IgD are expressed by these cells.
- T cells that do not recognize self-MHC are deleted in the thymus (Positive selection). Those that do recognize self-MHC and strongly bind self antigen are deleted as well (Negative selection).

Anergy and tolerance

- A self-reactive CD4 cell that weakly binds to self-antigen differentiates into a regulatory cell when presented with that antigen. They then secrete cytokines to prevent other cells from reacting to that antigen. Express CD 25 (α-chain of IL-2R) and FOXP3 transcription factor.
- T suppressor cells co-express CD24 and CD25.
- CD8 cells become anergic if not co-stimulated with CD80/CD86 required for activation.
- Those self-reactive T cells that do not encounter its antigen die from lack of stimulation.

Self antigens

- Autoimmune diseases result from reactions against antigens expressed by host tissue ("self antigens")
- Self antigens include:
- MHC I antigens
- MHC II antigens
- Nuclear antigens (e.g., centromere)
- Cytoplasmic antigens
- Immature self-reactive B and T cells are removed at their maturation sites (central tolerance)
- Self-reactive cells that escape maturation sites are neutralized in peripheral tissues (peripheral tolerance) and become anergic

Central tolerance (B cells)

- B cell specificity is determined by recombination events
- Create a large repertoire of antigen receptors
- Cells reacting with self-antigen are removed.
- Clonal deletion
- B cells undergo receptor editing of the light chain in the bone marrow.
- If that editing fails to prevent recognition and binding of innate (self) proteins, the B cell is deleted. (Negative selection)
- If the B cell escapes deletion and is weakly binding
- Is non-functional unless presented with high antigen concentration.

B-cell Tolerance

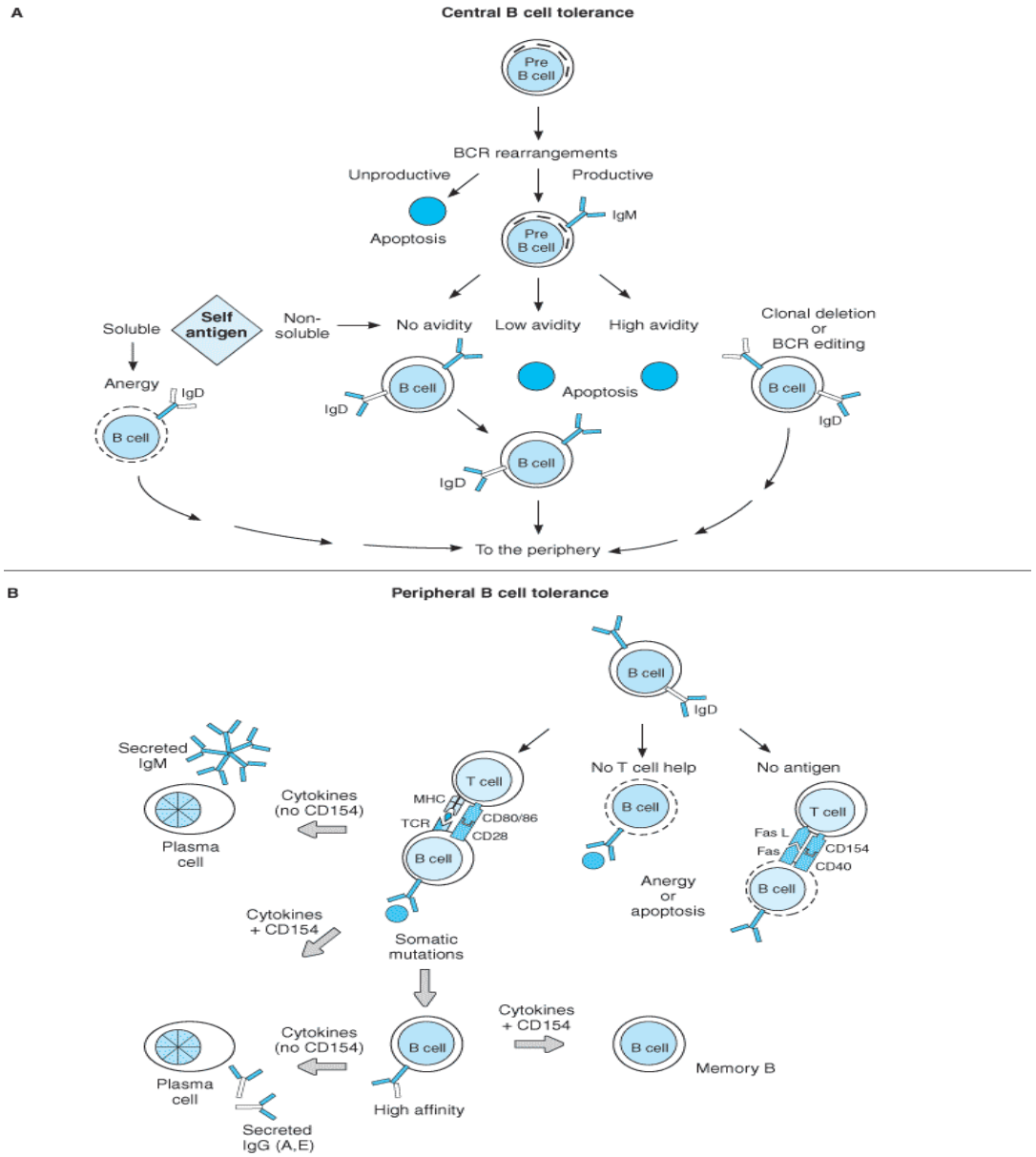


Fig. 3-6 Accessed 07/01/2010

Peripheral tolerance (B cells)

- If the B cell escapes deletion and is strongly binding and recognizes the antigen in the absence of co-stimulatory molecules
- Are stimulated to become permanently anergic
- Decreased levels of IgM and IgD are expressed by these cells.

Central tolerance (T cells)

- T cell specificity is determined by recombination events
- Create a large repertoire of antigen receptors
- Cells reacting with self-antigen are removed.
- T cells that do not recognize self-MHC are deleted in the thymus (Positive selection).
- Those that do recognize self-MHC and strongly bind self antigen are deleted as well (Negative selection).

T-cell Tolerance

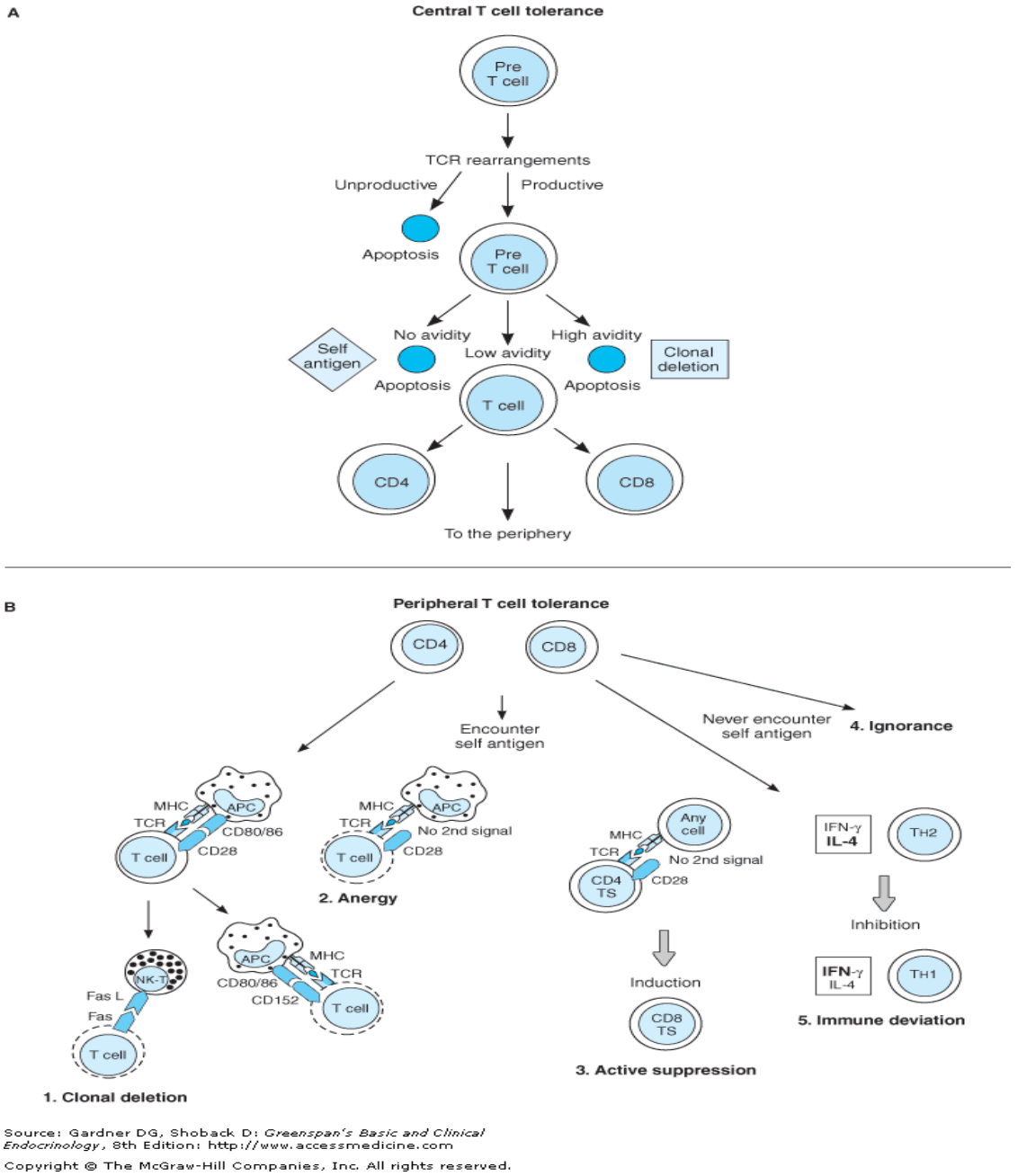


Fig. 3-5 Accessed 07/01/2010

Peripheral tolerance (T cells)

- A self-reactive CD4 cell that weakly binds to self-antigen differentiates into a T regulatory cell (T_{reg}) when presented with that antigen.
- Secrete cytokines to prevent other cells from reacting to that antigen.
- Express CD 25 (α-chain of IL-2R) and FOXP3 transcription factor.
- Fetal antigens induce long lasting FOXP3+ (Treg) cells that maintain fetal viability

Peripheral tolerance (T cells)

- T suppressor cells co-express CD24 and CD25.
- CD8 cells become anergic if not co-stimulated.
- CD80/CD86 required for activation.
- Those self-reactive T cells that do not encounter its antigen die from lack of stimulation.
- CLTA-4 is an inhibitory receptor that binds with high affinity to B7 ligands on antigen processing cells (APC).
- CD28 present on T suppressor cells has low B7 binding affinity.
- When APC presents self-antigen and little B7 expressed, CTLA-4 binds preferentially, rendering T cell functionally unresponsive (anergy)

Peripheral tolerance (T cells)

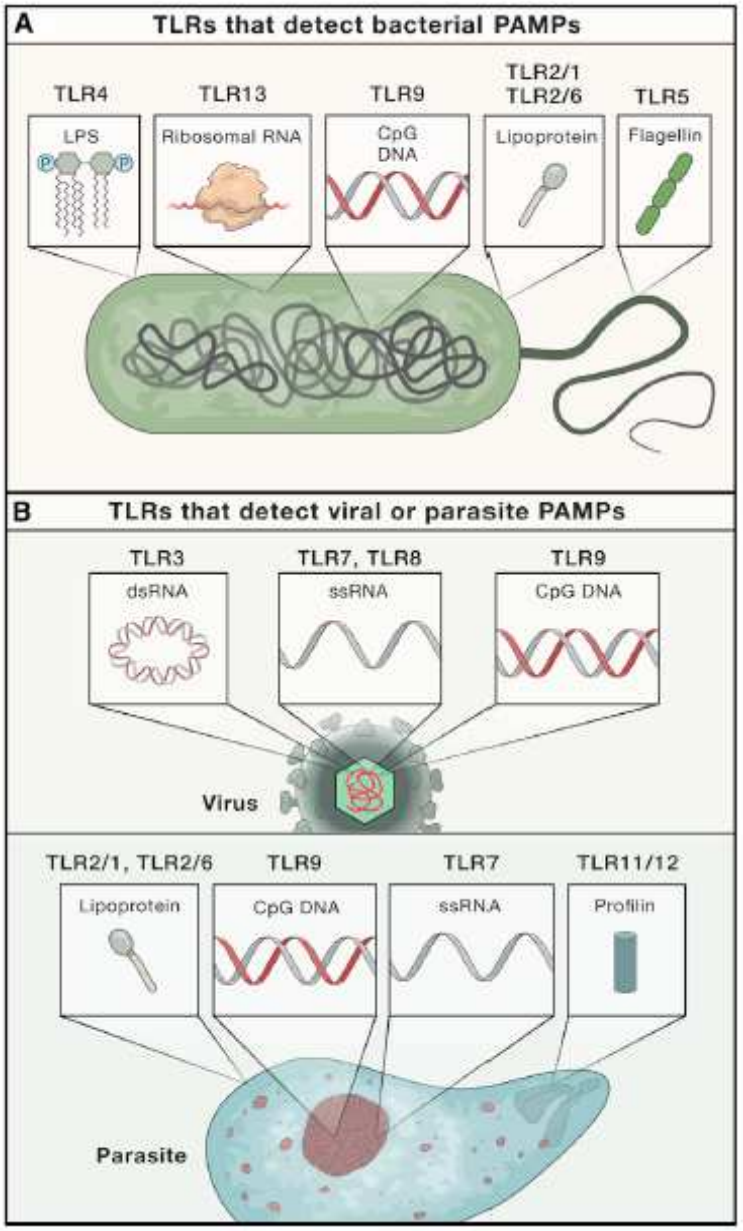
- If T cells recognize self-antigen, may express the pro-aptotic BIM without other members of the BCL family.
- Apoptosis via the mitochondrial pathway
- Both CD4+ and B cells express CD95 (FAS), a member of the TNF family
- FAS-ligand is structurally homologous to TNF
- Present on activated T lymphocytes
- If self-antigens engage antigen receptors of self-reactive T cells, both FAS and FAS-L are expressed, leading to apoptosis

Innate immunity

- Non-specific defense against microbial pathogens
- Does not confer long-lasting immunity against pathogens
- Cells involved
- Phagocytic cells
- Neutrophils and monocytes
- Macrophages and microglial cells
- NK cells
- Antigen processing cells (APC)
- Langham's cells and
- Mast cells
- Complement

Pattern recognition receptors

- Recognize ligands that are commonly expressed by microbial organisms (pathogen associated molecular patterns)
- Toll-like receptors
- Recognize molecules released by injured and necrotic cells (damage associated molecular patterns) detect microbes in the cytoplasm
- Leukocytes
- Plasma membrane receptors detect extracellular microbes
- Endosomal receptors detect ingested microbes
- Cytosolic receptors



Fitzgerald and Kagan, Toll-like Receptors and the Control of Immunity, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.041 Figure 1
Accessed 03/10/2020

Toll-like receptors

Present in plasma membrane and endosomal vesicles

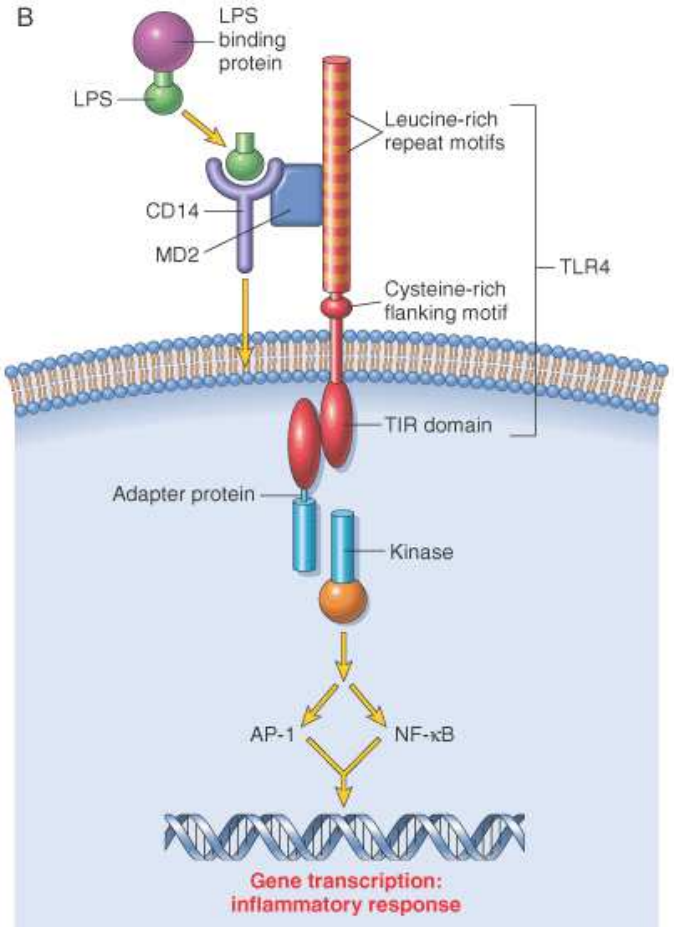
Binding activates NF-kB and AP-1

Stimulates synthesis and secretion of
- Inflammatory cytokines
  - TNF
  - IL-1
- Selectins (neutrophil adhesion)
- Interferon regulatory factors

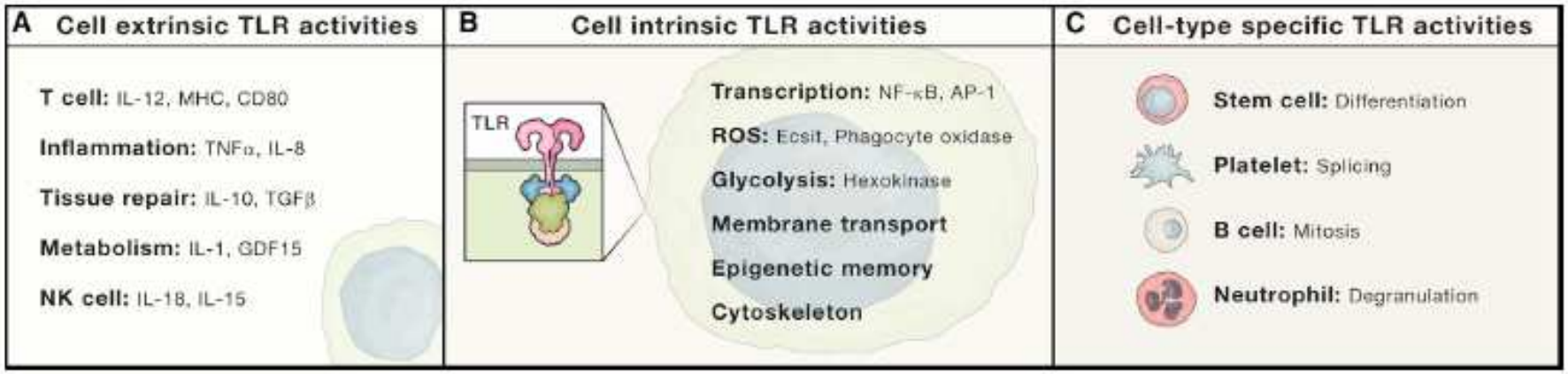
A

TLR	Ligand	Microbial source
TLR2	Lipoproteins Peptidoglycan Zymosan LPS GPI anchor Lipoarabinomannan Phosphatidylinositol dimannoside	Bacteria Gram positive bacteria Fungi Leptospira Trypanosomes Mycobacteria Mycobacteria
TLR3	Double-stranded RNA	Viruses
TLR4	LPS HSF00	Gram negative bacteria Chlamydia
TLR5	Flagellin	Various bacteria
TLR6	CpG DNA	Bacteria, protozoans

B



Burmester, GR, Pezzutto, A, Color Atlas of Immunology. 2003. Thieme. Stuttgart. P211 Accessed 12/10/2019



Fitzgerald and Kagan, Toll-like Receptors and the Control of Immunity, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.041 Figure 2
Accessed 03/10/2020

Supramolecular organizing center

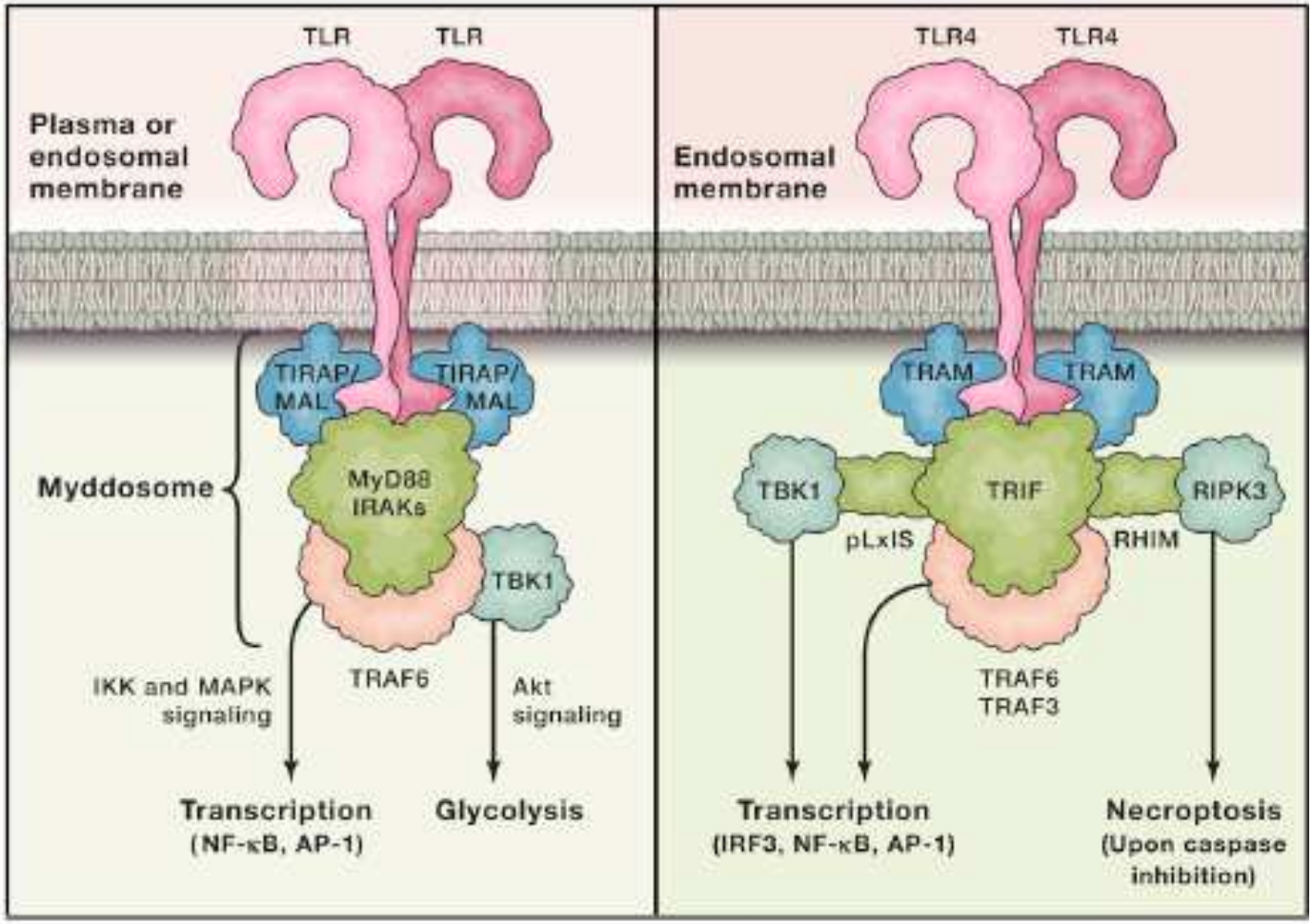
- All TLRs, except TLR3, induce the assembly of a supramolecular organizing center (SMOC), called the myddosome, upon PAMP detection.

Myddosome

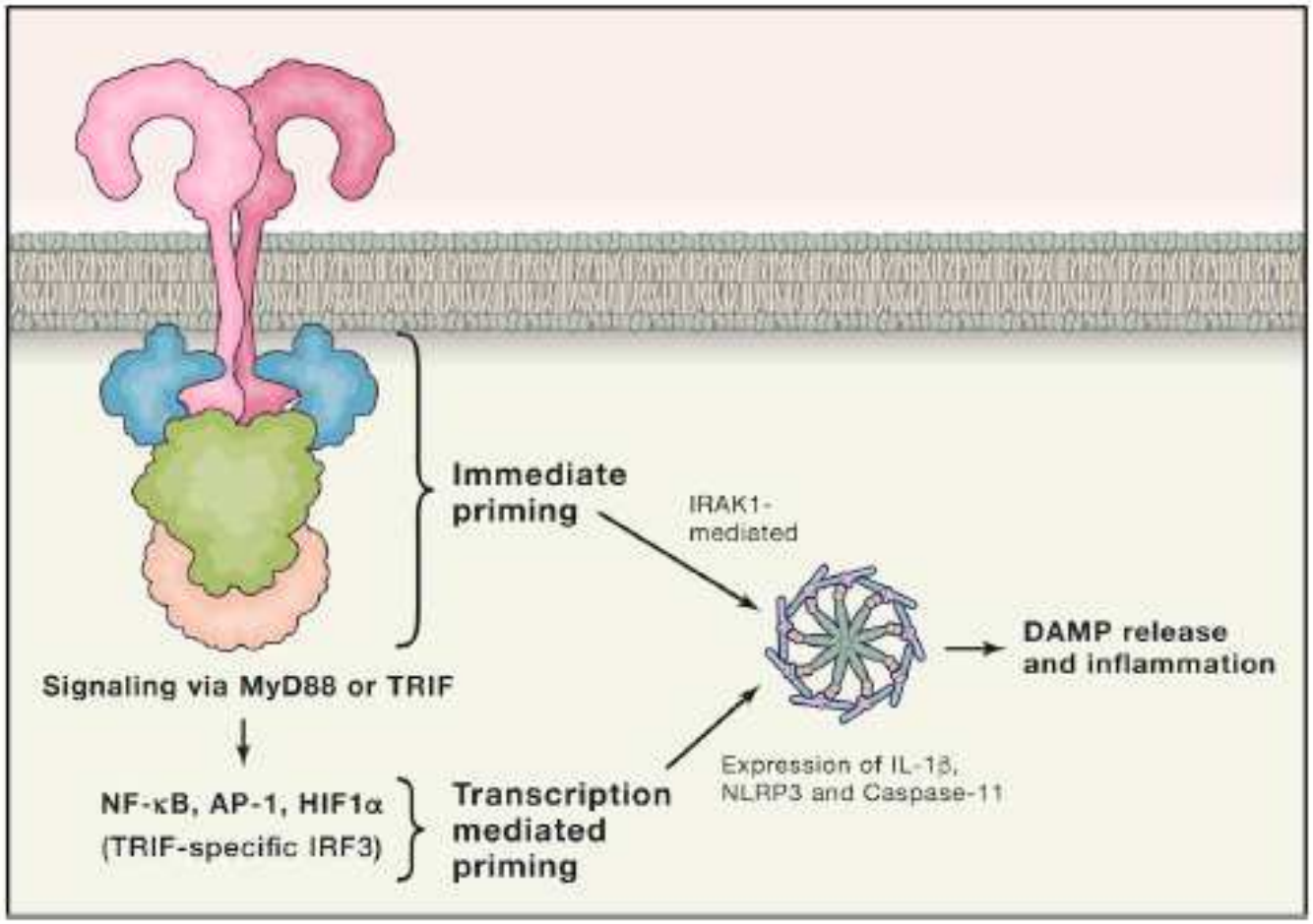
- Myddosome assembly occurs around the cytosolic tail of dimerized TLRs present at the plasma membrane or endosomes.
- The enzyme TRAF6 is present in the myddosome.
- TRAF6 functions to stimulate myddosome-associated TBK1 to drive metabolic changes in the cell and functions to stimulate IKK- and MAPK-dependent transcription factors.
- The collection of these activities promotes inflammation and host defense.

Triffosome

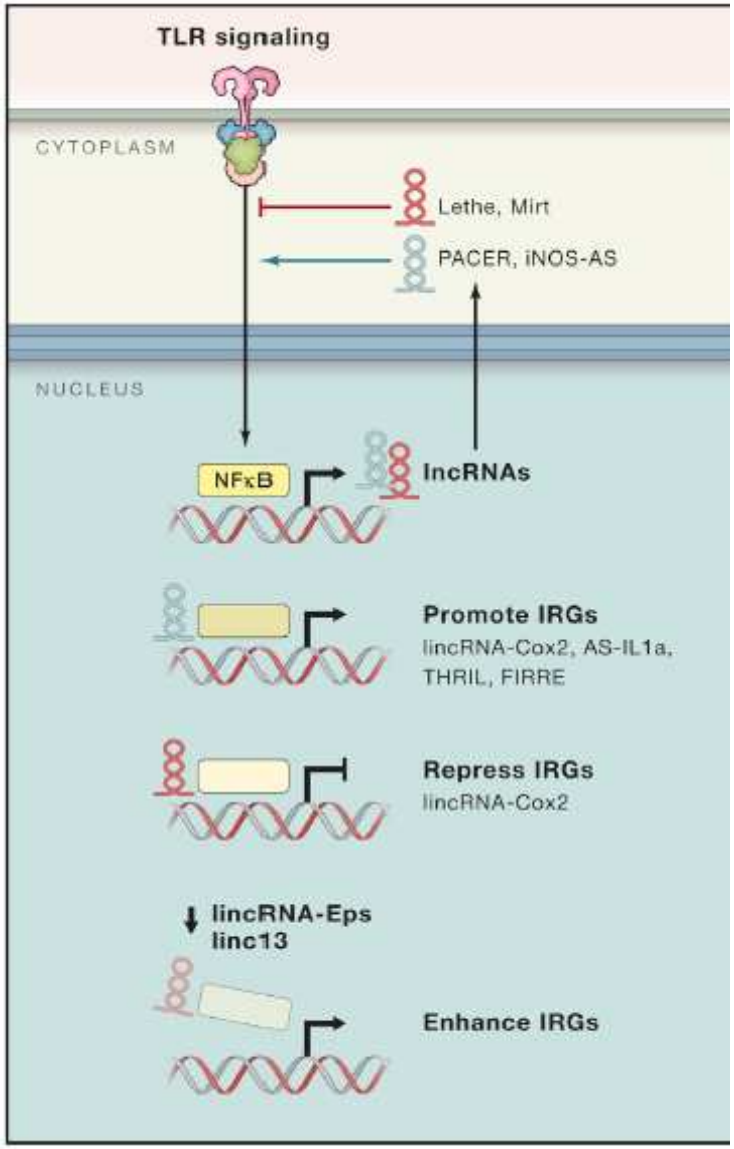
- On endosomes, TLR4 and TLR3 have the capacity to engage a SMOC called the triffosome.
- TRIF contains a pLxIS motif that promotes TBK1-dependent gene expression and a RHIM domain to promote RIPK3-dependent necroptosis.
- This latter activity only occurs upon conditions of caspase inhibition.



Fitzgerald and Kagan, Toll-like Receptors and the Control of Immunity, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.041 Figure 3
Accessed 03/10/2020



Fitzgerald and Kagan, Toll-like Receptors and the Control of Immunity, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.041 Figure 4
Accessed 03/10/2020



Fitzgerald and Kagan, Toll-like Receptors and the Control of Immunity, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.041 Figure 5 Accessed 03/10/2020

Regulation of the innate immune response

- TLR stimulation leads to temporally regulated changes in the expression of a number of lncRNAs
- lncRNAs can function in the cytosol or nucleus by binding proteins to either promote or restrain responses
- The lincRNA-Cox2 interacts with the SWI/SNF chromatin remodeling complex
- Regulate expression of immune genes that require chromatin remodeling for their expression.
- The lincRNA-Cox2 can interact with hnRNP A2/B1 to downregulate chemokine expression.

Regulation of the innate immune response

- iNOS-AS functions as a positive regulator of immune gene expression.
- The iNOS antisense transcript localizes to the cytoplasm
- Promotes the stability and subsequent translation of iNOS mRNA through direct base-pair complementation.

Regulation of the innate immune response

- Lethe and Mirt are induced lncRNAs that inhibit NFkB function.
- Lethe binds RelA to sequester NFkB
- Mirt2 acts indirectly by reducing Lys63 (K63)-linked ubiquitination of TRAF6, a key regulator of NFkB activation.
- Some lncRNAs are expressed in myeloid cells in the absence of stimulation and can
- be downregulated upon TLR activation.
- These lncRNAs can restrain immune gene expression by regulating chromatin accessibility
- Inc13 or lincRNAEps

Pattern recognition receptors

- Leukocytes containing NOD-like receptors
- Recognize uric acid
- Released ATP
- Loss of K^+
- Signal via cytoplasmic multiprotein complex (inflammasome)
- Activates capsase-1
- Generates IL-1
- Gain of function mutation associated with periodic fevers (autoinflammatory syndromes)

Pattern recognition receptors

- C-type lectin receptors
- Expressed on plasma membrane of macrophages and dendritic cells
- Detect fungal glycans
- RIG-like receptors
- Detect viral nucleic acid of viruses that replicate in the cytoplasm

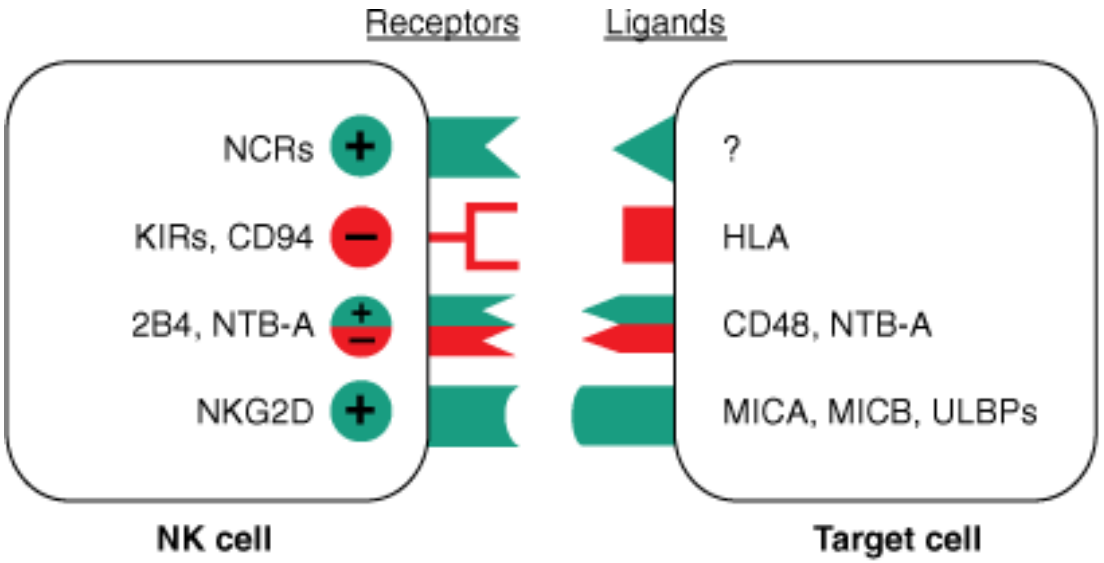
Pattern recognition receptors

- G protein-coupled receptors
- Leukocytes and macrophages
- Recognize N-formylmethionyl residues of bacterial peptides
- Mannose receptors
- Recognize terminal mannose on microbial sugars
- Induce phagocytosis

Infectious agent related disorders

- Rheumatic fever.
- IgG antibody to M-protein of Streptococcus pyogenes (Group A) cross reacts with heart tissue.
- Molecular mimicry.
- Reactive arthritis
- Chlamydia trachomatis (Reiter's syndrome)
- Borellia burgdorferi (Lyme disease)
- Salmonella
- Shigella
- Yersinia
- Campylobacter

NK cell receptor activation



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Fig. 308-4 Accessed 07/01/2010

NK cells

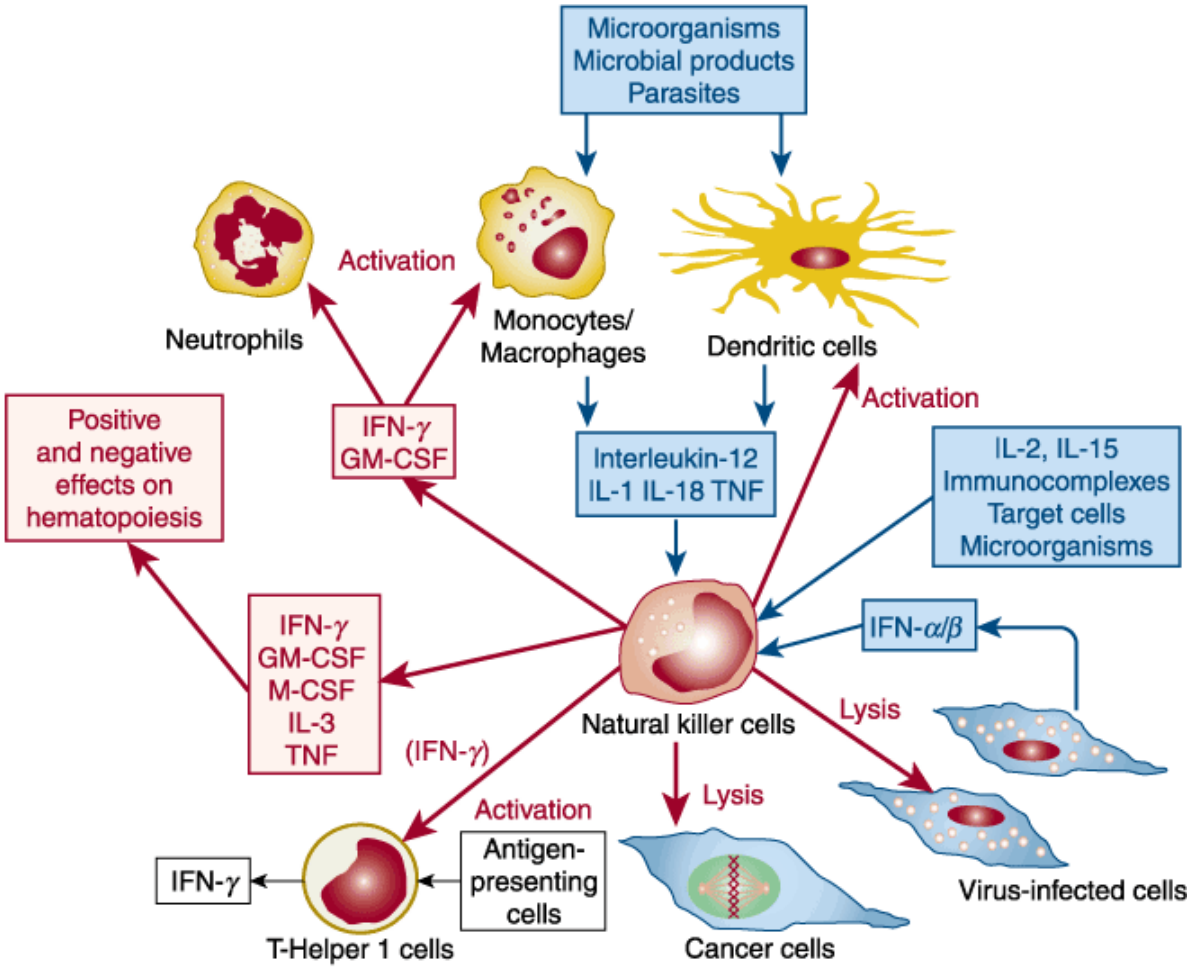
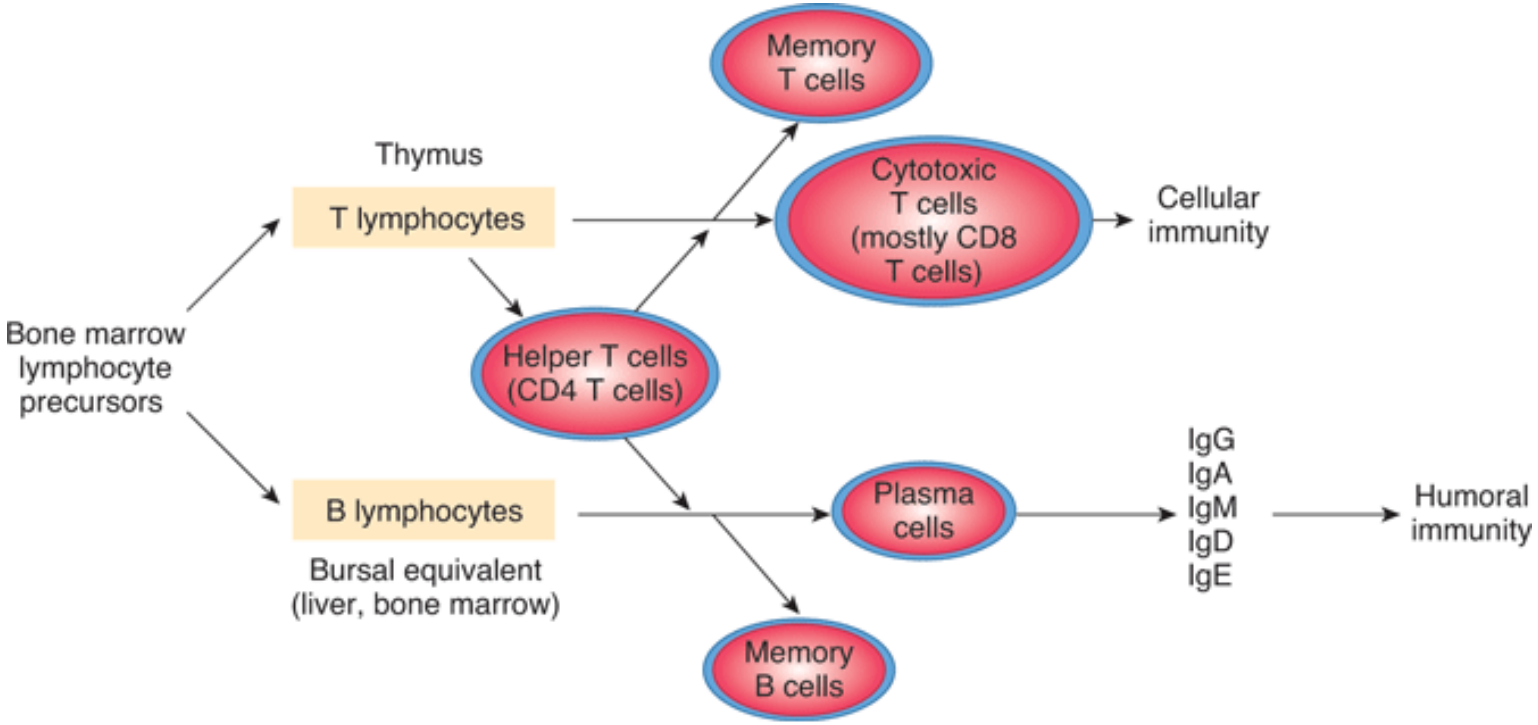


Fig.79-2 Accessed 07/01/2010

Acquired immunity

- Antigen dependent activation and expansion of lymphocytes
- B cells (humoral immunity)
- IgM synthesis begins at birth
- IgG synthesis begins about 6 weeks after birth
- Residual circulating maternal IgG transferred via placenta is humoral defense of newborn
- T cells (cellular immunity)
- MHC related

Mediation of immunity



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 3-5 Accessed 07/01/2010

Acquired immune response

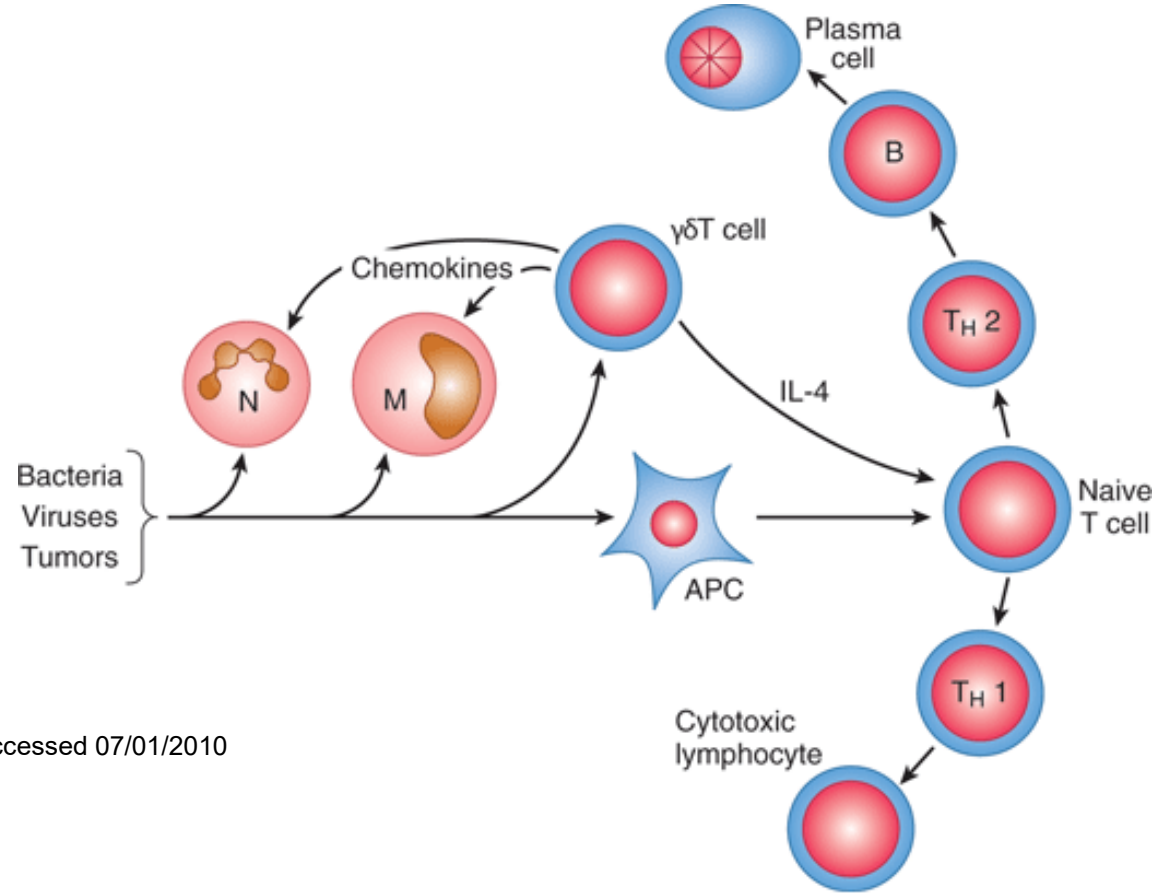
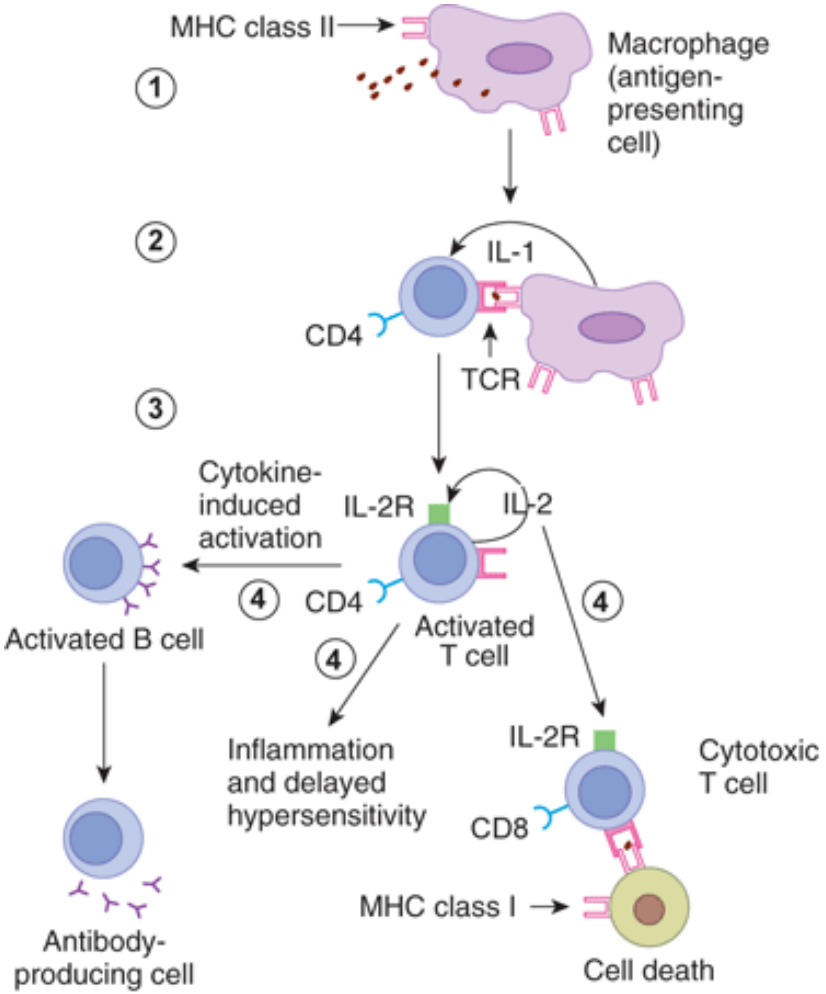


Fig. 3-3 Accessed 07/01/2010

Antigen presentation (old model)

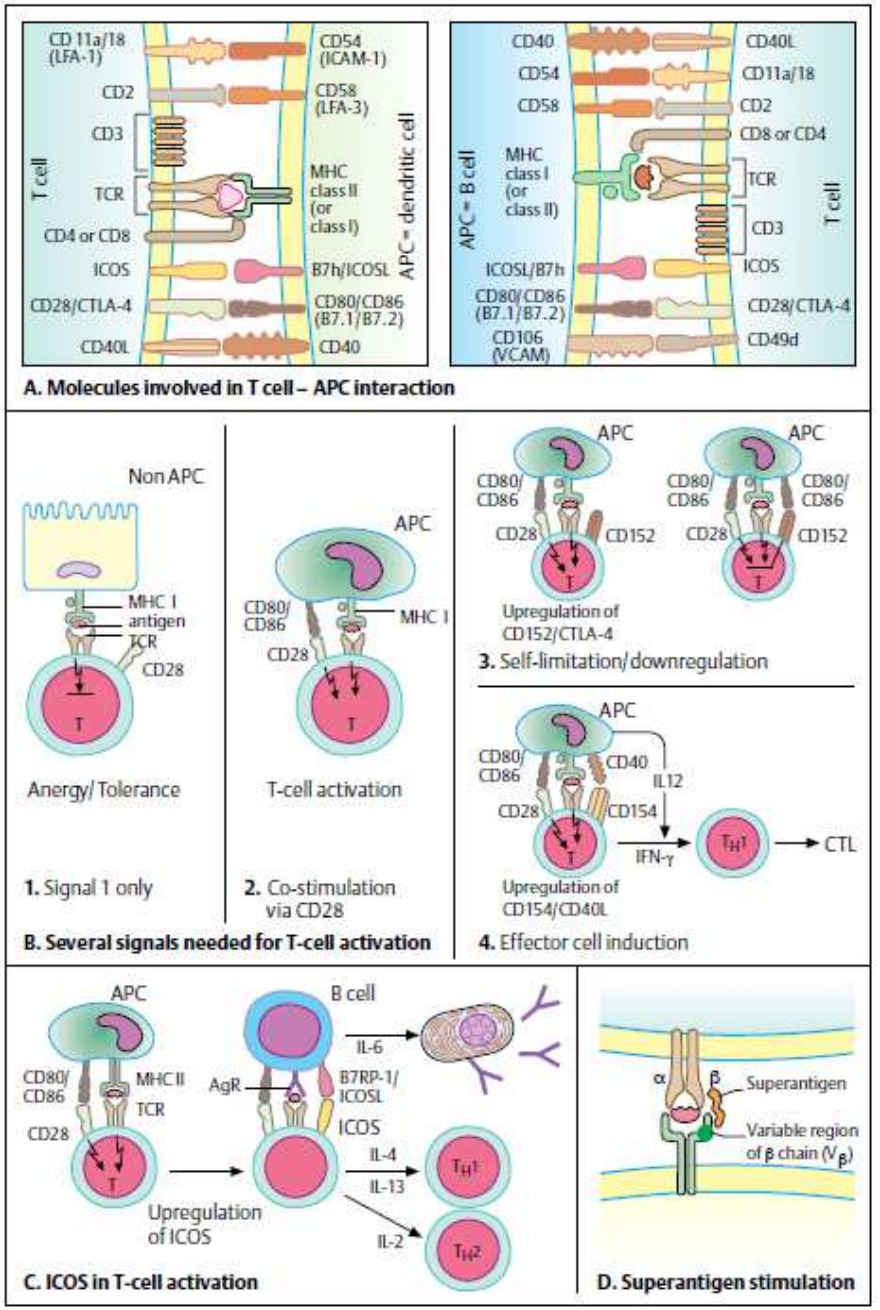


Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(Reproduced with permission from McPhee SJ, Lingappa VR, Ganong WF (editors): *Pathophysiology of Disease,* 4th ed. McGraw-Hill, 2003.)

Fig. 3-9 Accessed 07/01/2010

T-cell – APC interaction
(old model)



Burmester, GR, Pezzutto, A, Color Atlas of Immunology. 2003. Thieme. Stuttgart. p59 Accessed 12/10/2019

Antigen presentation (new model)

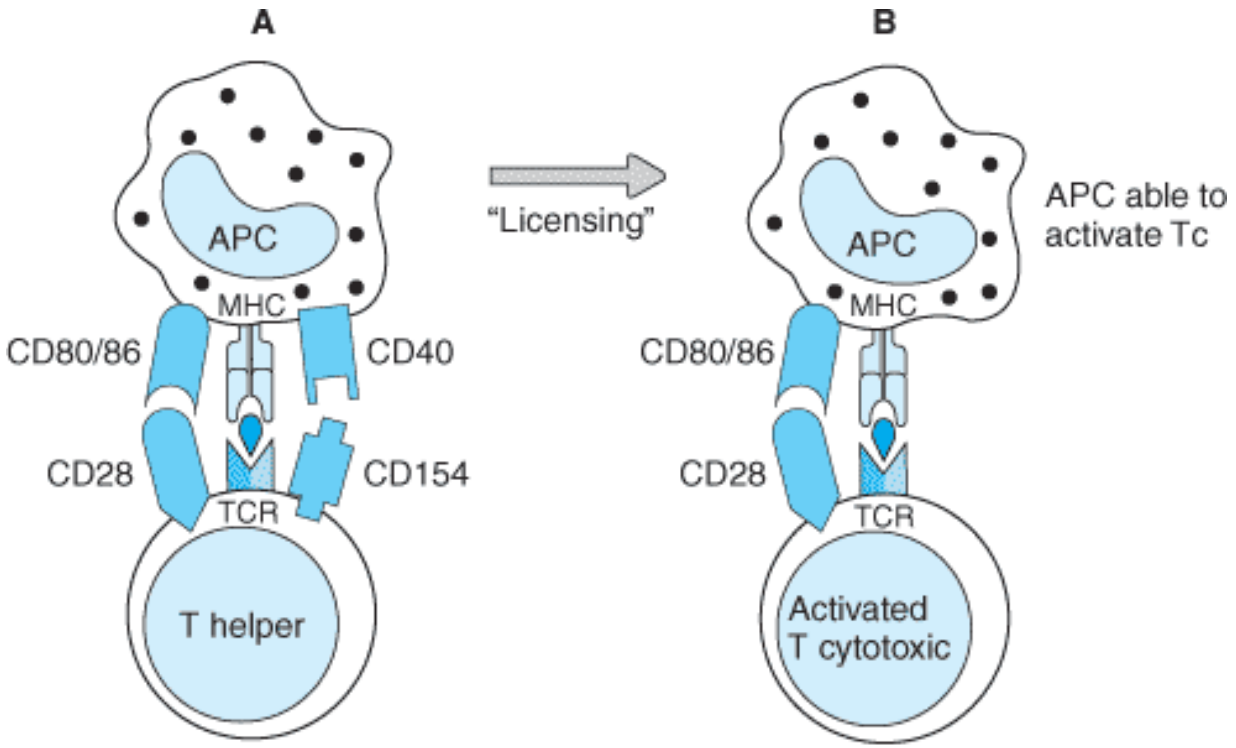
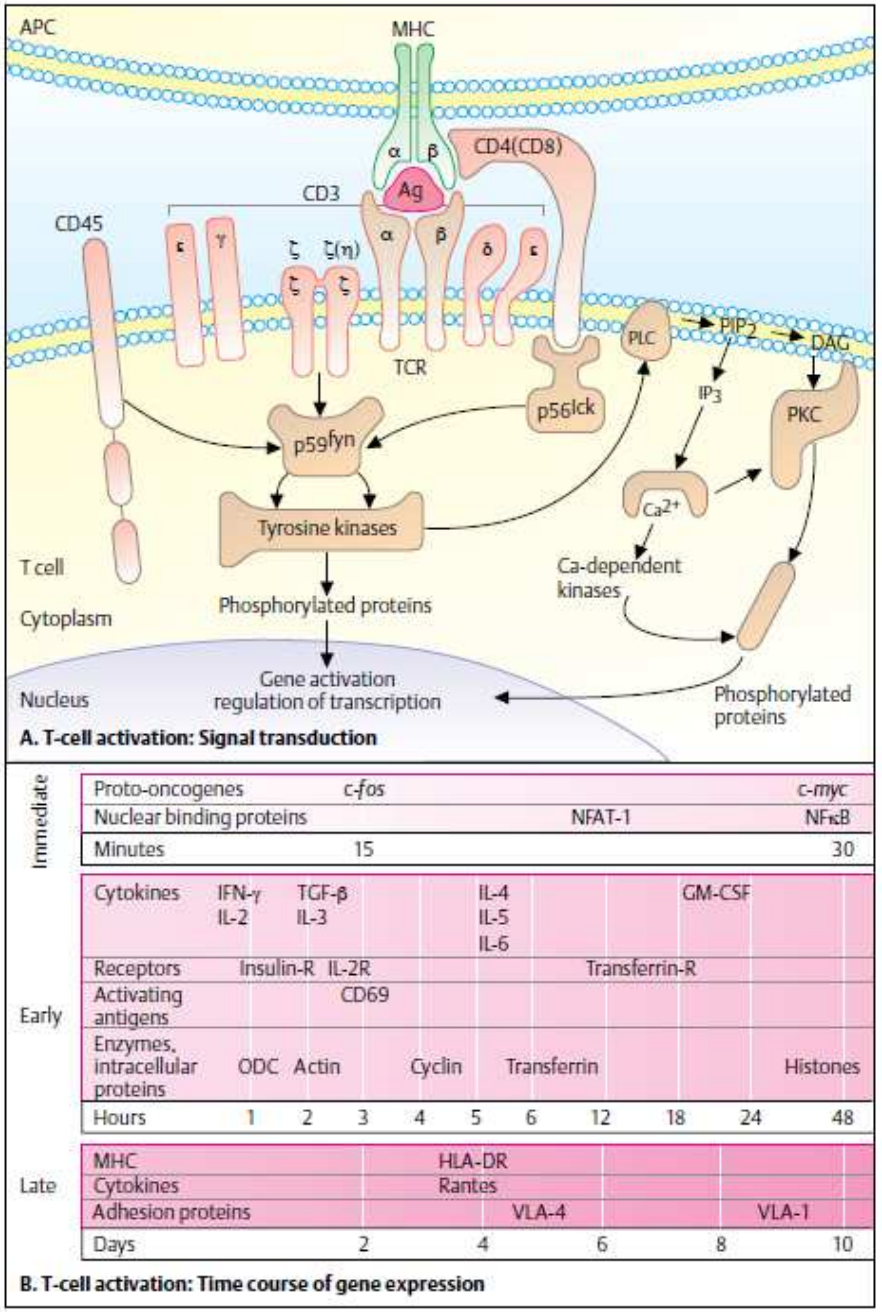


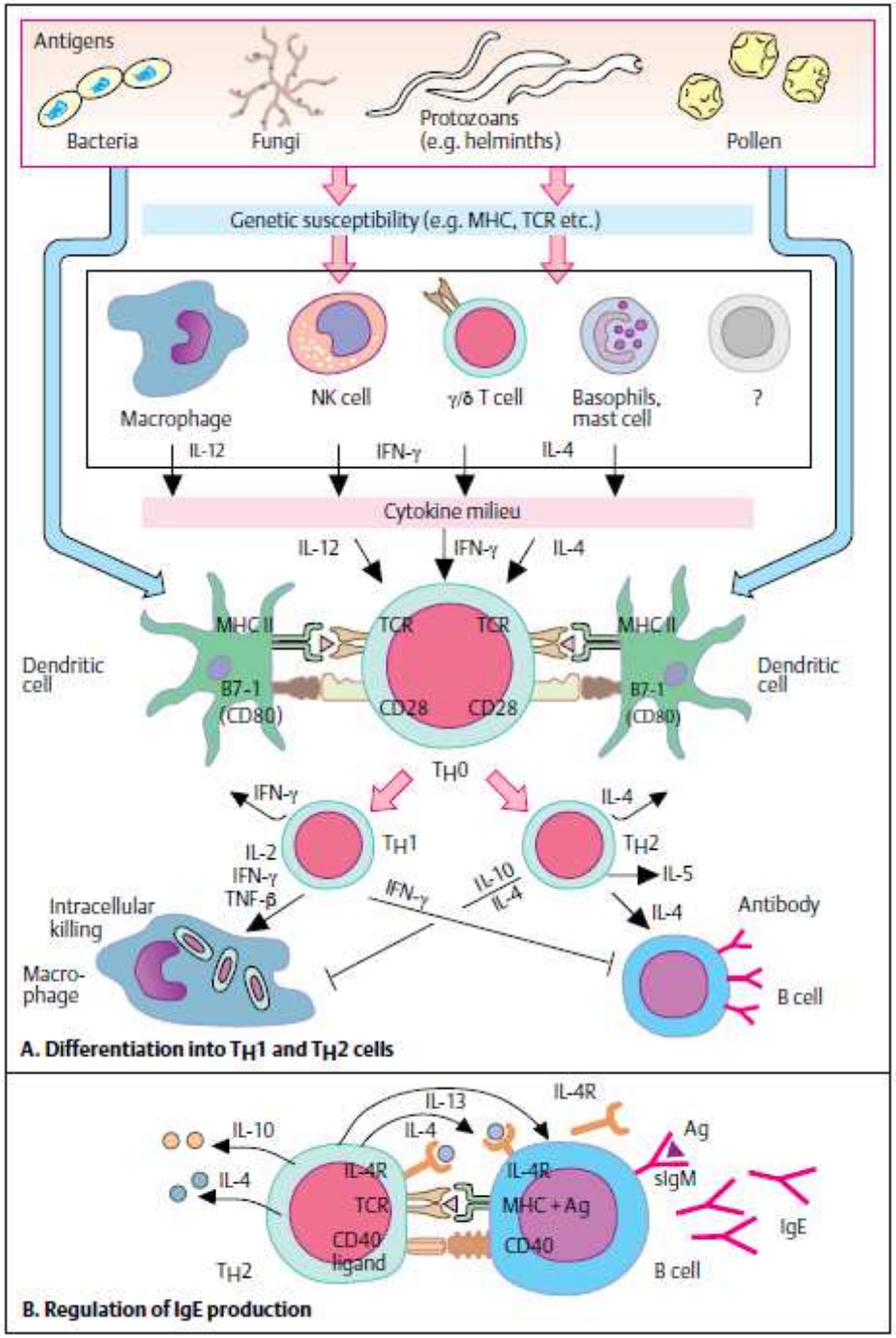
Fig. 3-4 Accessed 07/01/2010

T-cell activation

Burmester, GR, Pezzutto, A, Color Atlas of Immunology. 2003. Thieme. Stuttgart. p19 Accessed 12/10/2019

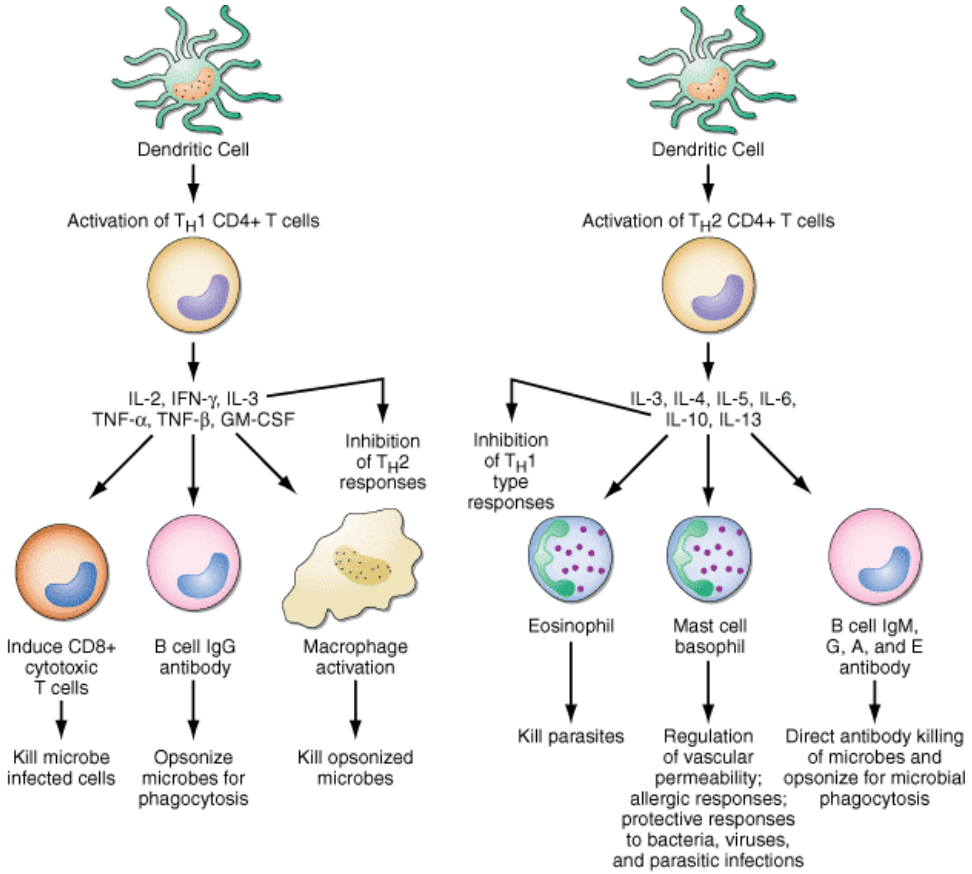


T-cell differentiation



Burmester, GR, Pezzutto, A, Color Atlas of Immunology. 2003. Thieme. Stuttgart. P21
Accessed 12/10/2019

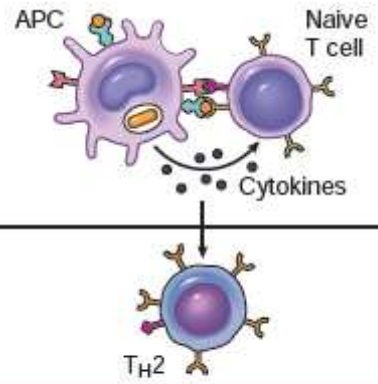
CD4+ cell classes



Adapted from S Romagnani: CD4 effector cells, in J Gallin, R Snyderman (eds): Inflammation: Basic Principles and Clinical Correlates, 3d ed. Philadelphia, Lippincott Williams & Wilkins, 1999; with permission.)

Fig. 308-2
Accessed 07/01/2010

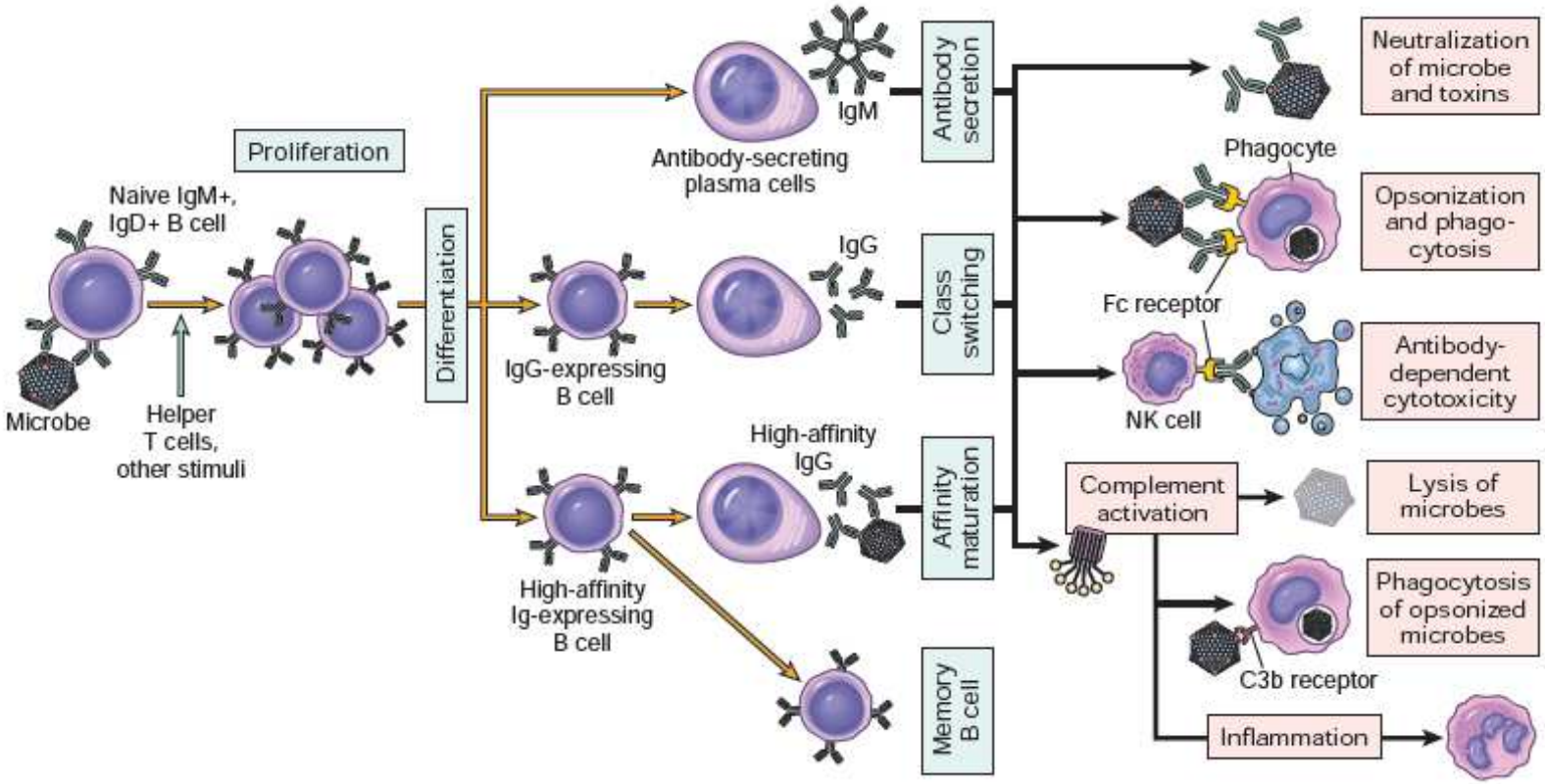
T-cell produced cytokines



	T_H1	T_H2	T_H17
Major cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22
Cytokines that induce this subset	IFN-γ, IL-12	IL-4	TGF-β, IL-6, IL-1, IL-23
Immunological reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, granulomatous inflammation)	Allergies	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, MS)

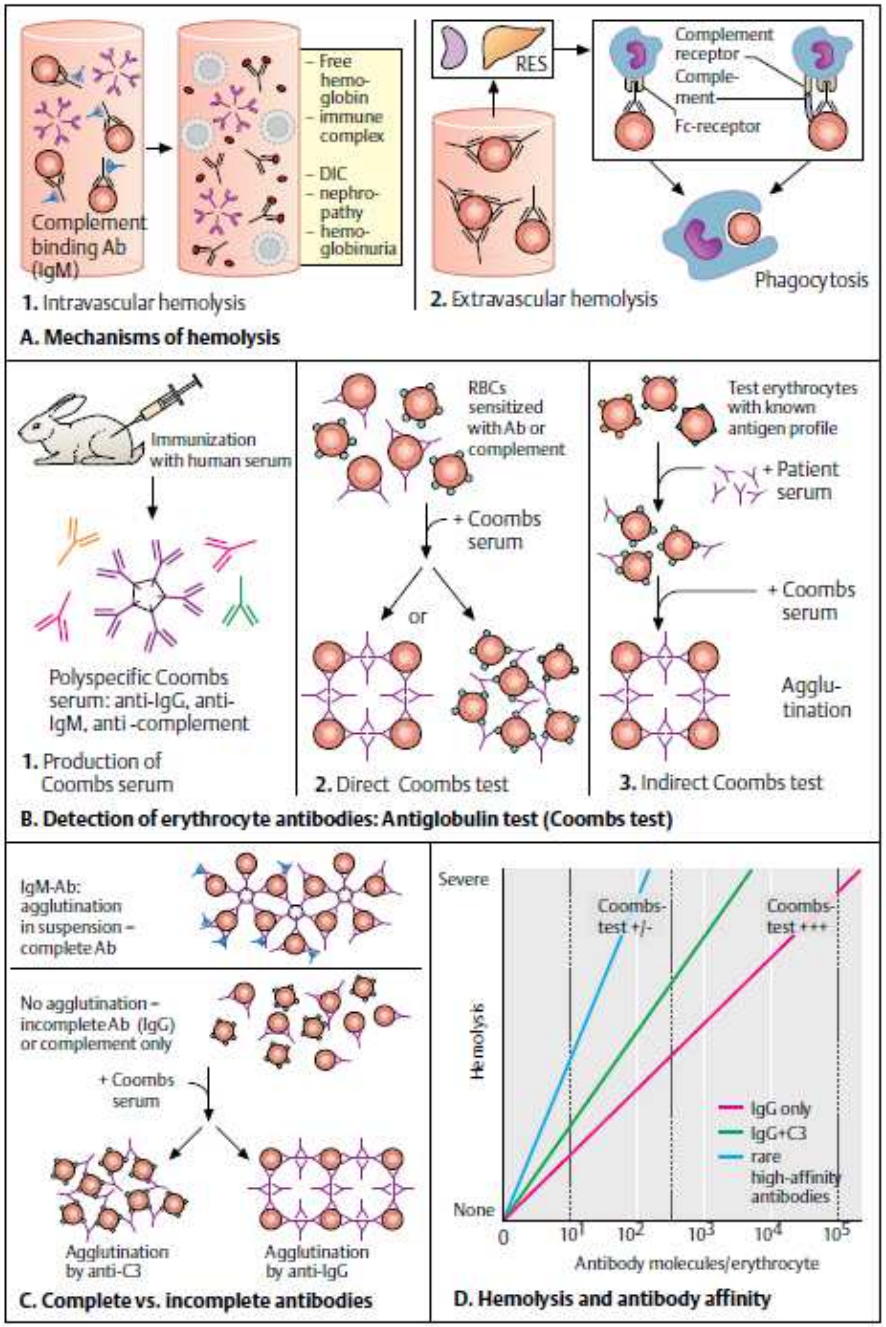
Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig 6-11 Accessed 12/10/2019

Immune expression



Kumar, V, Abbas, AK, Aster, JC, "Diseases of the immune system," in Kumar, V, Abbas, AK, Aster, JC(eds). Robbins and Cotran Pathological Basis of Disease 2015. Elsevier. Philadelphia. Fig 6-12 Accessed 12/10/2019

Immune mediated hemolysis



Burmester, GR, Pezzutto, A, Color Atlas of Immunology. 2003. Thieme. Stuttgart. p119 Accessed 12/10/2019